09/108,673
AH A25

1. Document ID: US 6184212 B1

L7: Entry 1 of 42

File: USPT

Feb 6, 2001

US-PAT-NO: 6184212
DOCUMENT-IDENTIFIER: US 6184212 B1
TITLE: Antisense modulation of human mdm2 expression
DATE-ISSUED: February 6, 2001

US-CL-CURRENT: 514/44; 435/325, 435/375, 435/6, 435/91.1, 536/23.1, 536/24.3, 536/24.33, 536/24.5

APPL-NO: 9/ 280805
DATE FILED: March 26, 1999

PARENT-CASE:
This application is a continuation in-part of applicaton Ser. No. 09/048,810 filed Mar. 26, 1998.

IN: Miraglia; Loren J., Nero; Pamela, Graham; Mark J., Monia; Brett P., Cowsert; Lex M.

AB: Compounds, compositions and methods are provided for inhibiting the expression of human mdm2. The compositions include antisense compounds targeted to nucleic acids encoding mdm2. Methods of using these oligonucleotides for inhibition of mdm2 expression and for treatment of diseases such as cancers associated with overexpression of mdm2 are provided.

L7: Entry 1 of 42

File: USPT

Feb 6, 2001

DOCUMENT-IDENTIFIER: US 6184212 B1
TITLE: Antisense modulation of human mdm2 expression

BSPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8:91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7:1). One or more penetration enhancers from one or more of these broad categories may be included. Compositions comprising oligonucleotides and penetration enhancers are disclosed in co-pending U.S. patent application Ser. No. 08/886,829 to Teng et al., filed Jul. 1, 1997, which is herein incorporated by reference in its entirety.

2. Document ID: US 6180403 B1

L7: Entry 2 of 42

File: USPT

Jan 30, 2001

US-PAT-NO: 6180403
DOCUMENT-IDENTIFIER: US 6180403 B1
TITLE: Antisense inhibition of tumor necrosis factor alpha converting enzyme (TACE) expression
DATE-ISSUED: January 30, 2001

US-CL-CURRENT: 435/375; 435/325, 435/366, 435/6, 435/91.1, 536/23.1, 536/24.31, 536/24.33, 536/24.5

APPL-NO: 9/ 429093
DATE FILED: October 28, 1999

IN: Flournoy; Shin Cheng, Bennett; C. Frank

AB: Compositions and methods are provided for inhibiting the expression of human tumor necrosis factor-.alpha.-converting enzyme (TACE). Antisense oligonucleotides targeted to nucleic acids encoding TACE are preferred. Methods of using these oligonucleotides for inhibition of TACE expression and for treatment of diseases, particularly inflammatory and autoimmune diseases, associated with overexpression of TACE or TNF-.alpha. are provided.

L7: Entry 2 of 42

File: USPT

Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180403 B1
TITLE: Antisense inhibition of tumor necrosis factor alpha converting enzyme (TACE) expression

DEPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems 1991, 8, 91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems 1990, 7, 1-33). One or more penetration enhancers from one or more of hese broad categories may be included.

3. Document ID: US 6172216 B1

L7: Entry 3 of 42

File: USPT

Jan 9, 2001

US-PAT-NO: 6172216
DOCUMENT-IDENTIFIER: US 6172216 B1
TITLE: Antisense modulation of BCL-X expression
DATE-ISSUED: January 9, 2001

US-CL-CURRENT: 536/24.5; 435/325, 435/375, 435/6, 435/91.1, 536/23.1, 536/23.2, 536/24.3, 536/24.33

APPL-NO: 9/ 167921

DATE FILED: October 7, 1998

IN: Bennett; C. Frank, Dean; Nicholas M., Monia; Brett P., Nickoloff; Brian J., Zhang; QingQing

AB: Compositions and methods are provided for modulating the expression of bcl-x. Antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding bcl-x are preferred. Methods of using these compounds for modulation of bcl-x expression and for treatment of diseases associated with expression of bcl-x are also provided.

L7: Entry 3 of 42

File: USPT

Jan 9, 2001

DOCUMENT-IDENTIFIER: US 6172216 B1
TITLE: Antisense modulation of BCL-X expression

BSPR: Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration enhancers from one or more of these broad categories may be included.

4. Document ID: US 6171837 B1

L7: Entry 4 of 42

File: USPT

Jan 9, 2001

US-PAT-NO: 6171837
DOCUMENT-IDENTIFIER: US 6171837 B1
TITLE: Mouse and human 9-cis-retinol dehydrogenase
DATE-ISSUED: January 9, 2001

US-CL-CURRENT: 435/190; 536/23.2

APPL-NO: 8/ 940424
DATE FILED: September 29, 1997

IN: Blaner; William S., Zott; Roseann Piantedosi, Gamble; Mary V., Mertz; James R.

AB: This invention provides an isolated nucleic acid molecule (SEQ ID NO:1) encoding a human 9-cis-retinol dehydrogenase. Also provided is a 9-cis-retinol dehydrogenase encoded by the isolated nucleic acid molecule, wherein the 9-cis-retinol dehydrogenase comprises the amino acid sequence of SEQ. ID NO: 2. This invention also provides isolated nucleic acid molecules comprising the nucleotide sequence shown in any of SEQ. ID NOS: 6, 7, and 8 encoding mouse 9-cis-retinol dehydrogenases.

L7: Entry 4 of 42

File: USPT

Jan 9, 2001

DOCUMENT-IDENTIFIER: US 6171837 B1
TITLE: Mouse and human 9-cis-retinol dehydrogenase

DEPR: The above-described oligonucleotides or compounds which are determined to be potentially therapeutic can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents, for example, enough saline or glucose to make the solution isotonic, bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

5. Document ID: US 6165788 A

L7: Entry 5 of 42

File: USPT

Dec 26, 2000

US-PAT-NO: 6165788
DOCUMENT-IDENTIFIER: US 6165788 A
TITLE: Antisense modulation of Survivin expression
DATE-ISSUED: December 26, 2000

US-CL-CURRENT: 435/375; 435/377, 435/455, 435/6, 536/23.1, 536/24.1, 536/24.5

APPL-NO: 9/ 286407
DATE FILED: April 5, 1999

PARENT-CASE: FIELD OF THE INVENTION This application is a continuation-in-part of U.S. Ser. No. 09/163,162 filed Sep. 29, 1998. The present invention provides compositions and methods for modulating the expression of Survivin. In particular, this invention relates to antisense compounds, particularly oligonucleotides, specifically hybridizable with nucleic acids encoding human Survivin. Such oligonucleotides have been shown to modulate the expression of Survivin.

IN: Bennett; C. Frank, Ackermann; Elizabeth J., Swayze; Eric E., Cowsert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the expression of Survivin. The compositions comprise antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding Survivin. Methods of using these compounds for modulation of Survivin expression and for treatment of diseases associated with expression of Survivin are provided.

L7: Entry 5 of 42

File: USPT

Dec 26, 2000

DOCUMENT-IDENTIFIER: US 6165788 A
TITLE: Antisense modulation of Survivin expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7:1, 1-33). One or more penetration enhancers from one or more of these broad categories may be included.

6. Document ID: US 6159694 A

L7: Entry 6 of 42
File: USPT
Dec 12, 2000

US-PAT-NO: 6159694
DOCUMENT-IDENTIFIER: US 6159694 A
TITLE: Antisense modulation of stat3 expression
DATE-ISSUED: December 12, 2000

US-CL-CURRENT: 435/6; 435/325, 435/91.1, 536/23.1, 536/24.3, 536/24.5

APPL-NO: 9/ 288461
DATE FILED: April 8, 1999

IN: Karras; James G.

AB: Compounds, compositions and methods are provided for inhibiting the expression of human STAT3. The compositions comprise antisense oligonucleotides targeted to nucleic acids encoding STAT3. Methods of using these oligonucleotides for inhibition of STAT3 expression and for treatment of diseases, particularly inflammatory diseases and cancers, associated with overexpression or constitutive activation of STAT3 are provided.

L7: Entry 6 of 42
File: USPT
Dec 12, 2000

DOCUMENT-IDENTIFIER: US 6159694 A
TITLE: Antisense modulation of stat3 expression

BSPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides.
Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration enhancers from one or more of these broad categories may be included. Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, recinleate, monoolein (a.k.a. 1-monooleoyl-rac-glycerol), dilaurin, caprylic acid, arachidonic acid, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, mono- and di-glycerides and physiologically acceptable salts thereof (i.e., oleate, laurate, caprate, myristate, palmitate, stearate, linoleate, etc.) (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, page 92; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1; El-Hariri et al., J. Pharm. Pharmacol., 1992 44, 651-654).

7. Document ID: US 6140124 A

L7: Entry 7 of 42
File: USPT
Oct 31, 2000

US-PAT-NO: 6140124
DOCUMENT-IDENTIFIER: US 6140124 A
TITLE: Antisense modulation of P38 mitogen activated protein kinase expression
DATE-ISSUED: October 31, 2000

US-CL-CURRENT: 435/375; 435/325, 435/6, 435/91.1, 536/23.1, 536/24.3, 536/24.31, 536/24.33, 536/24.5

APPL-NO: 9/ 286904
DATE FILED: April 6, 1999

IN: Monia; Brett P., Gaarde; William A., Nero; Pamela S., McKay; Robert

AB: Compositions and methods for the treatment and diagnosis of diseases or conditions amenable to treatment through modulation of expression of a gene encoding a p38 mitogen-activated protein kinase (p38 MAPK) are provided. Methods for the treatment and diagnosis of diseases or conditions associated with aberrant expression of one or more p38 MAPKs are also provided.

L7: Entry 7 of 42
File: USPT
Oct 31, 2000

DOCUMENT-IDENTIFIER: US 6140124 A
TITLE: Antisense modulation of P38 mitogen activated protein kinase expression

BSPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may include penetration enhancers in order to enhance the alimentary delivery of the

oligonucleotides.
Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty
acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical
Reviews in Therapeutic Drug Carrier Systems, 1991, 8:91-192; Muranishi, Critical Reviews in
Therapeutic Drug Carrier Systems, 1990, 7:1). One or more penetration enhancers from one or more
of these broad categories may be included.

8. Document ID: US 6136603 A

L7: Entry 8 of 42
File: USPT
Oct 24, 2000

US-PAT-NO: 6136603
DOCUMENT-IDENTIFIER: US 6136603 A
TITLE: Antisense modulation of interleukin-5 signal transduction
DATE-ISSUED: October 24, 2000

US-CL-CURRENT: 435/375; 435/366, 435/6, 435/91.1, 536/23.1, 536/24.31, 536/24.33, 536/24.5

APPL-NO: 9/ 280799
DATE FILED: March 26, 1999

IN: Dean; Nicholas M., Karras; James G., McKay; Robert

AB: Compositions and methods are provided for antisense modulation of interleukin-5
signal transduction. Antisense compounds, particularly antisense oligonucleotides, targeted
to nucleic acids encoding interleukin-5 and interleukin-5 receptor.alpha. are preferred.
Methods of using these compounds for modulation of interleukin-5 signal transduction and for
treatment of diseases associated with interleukin-5 signal transduction are also provided.

L7: Entry 8 of 42
File: USPT
Oct 24, 2000

DOCUMENT-IDENTIFIER: US 6136603 A
TITLE: Antisense modulation of interleukin-5 signal transduction

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present
invention may also include penetration enhancers in order to enhance the alimentary delivery of
the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad
categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee
et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi,
Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration
enhancers from one or more of these broad categories may be included.

9. Document ID: US 6133246 A

L7: Entry 9 of 42
File: USPT
Oct 17, 2000

US-PAT-NO: 6133246
DOCUMENT-IDENTIFIER: US 6133246 A
TITLE: Antisense oligonucleotide compositions and methods for the modulation of JNK proteins
DATE-ISSUED: October 17, 2000

US-CL-CURRENT: 514/44; 435/183, 435/194, 435/325, 435/366, 435/375, 435/6, 536/23.1, 536/24.31,
536/24.5

APPL-NO: 9/ 287796
DATE FILED: April 7, 1999

PARENT-CASE:
This application is a continuation-in-part of U.S. application Ser. No. 09/130,616 filed Aug. 7,
1998 which is a continuation-in-part of U.S. application Ser. No. 08/910,629 filed Aug. 13, 1997,
now U.S. Pat. No. 5,877,309.

IN: McKay; Robert, Dean; Nicholas, Monia; Brett P., Nero; Pamela S., Gaarde; William
A.

AB: Compositions and methods for the treatment and diagnosis of diseases or disorders
amenable to treatment through modulation of expression of a gene encoding a Jun N-terminal
kinase (JNK protein) are provided. Oligonucleotide are herein provided which are
specifically hybridizable with nucleic acids encoding JNK1, JNK2 and JNK3, as well as other
JNK proteins and specific isoforms thereof. Methods of treating animals suffering from
diseases or disorders amenable to therapeutic intervention by modulating the expression of
one or more JNK proteins with such oligonucleotide are also provided. Methods for the
treatment and diagnosis of diseases or disorders associated with aberrant expression of one
or more JNK proteins are also provided. Methods for inducing apoptosis and for treating
diseases or conditions associated with a reduction in apoptosis are also provided.

L7: Entry 9 of 42
File: USPT
Oct 17, 2000

DOCUMENT-IDENTIFIER: US 6133246 A
TITLE: Antisense oligonucleotide compositions and methods for the modulation of JNK proteins

BSPR:
C. Penetration Enhancers: Pharmaceutical compositions comprising the oligonucleotides of the
present invention may also include penetration enhancers in order to enhance the alimentary
delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of
five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and
non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8,
91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7:1).

10. Document ID: US 6133031 A

L7: Entry 10 of 42

File: USPT

Oct 17, 2000

US-PAT-NO: 6133031
DOCUMENT-IDENTIFIER: US 6133031 A
TITLE: Antisense inhibition of focal adhesion kinase expression
DATE-ISSUED: October 17, 2000

US-CL-CURRENT: 435/375; 435/6, 435/91.1, 514/44, 536/23.1, 536/24.5

APPL-NO: 9/ 377310
DATE FILED: August 19, 1999

IN: Monia; Brett P., Gaarde; William A.

AB: Compounds, compositions and methods are provided for inhibiting FAK mediated signaling. The compositions comprise antisense compounds targeted to nucleic acids encoding FAK. Methods of using these antisense compounds for inhibition of FAK expression and for treatment of diseases, particularly cancers, associated with overexpression or constitutive activation of FAK are provided.

L7: Entry 10 of 42

File: USPT

Oct 17, 2000

DOCUMENT-IDENTIFIER: US 6133031 A
TITLE: Antisense inhibition of focal adhesion kinase expression

BSPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides.
Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems 1991, 8, 91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems 1990, 7, 1-33). One or more penetration enhancers from one or more of these broad categories may be included.

11. Document ID: US 6117847 A

L7: Entry 11 of 42

File: USPT

Sep 12, 2000

US-PAT-NO: 6117847
DOCUMENT-IDENTIFIER: US 6117847 A
TITLE: Oligonucleotides for enhanced modulation of protein kinase C expression

DATE-ISSUED: September 12, 2000

US-CL-CURRENT: 514/44; 435/375, 536/24.5

APPL-NO: 9/ 094714
DATE FILED: June 15, 1998

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application is a continuation-in-part of U.S. patent application Ser. No. 08/664,336 filed Jun. 14, 1996, now U.S. Pat. No. 5,922,686, which is a continuation-in-part of U.S. patent application Ser. No. 08/089,996, filed Jul. 9, 1993, which issued on Dec. 30, 1997 as U.S. Pat. No. 5,703,054, which in turn is a continuation-in-part of U.S. patent application Ser. No. 07/852,852 filed Mar. 16, 1992, now abandoned.

IN: Bennett; C. Frank, Dean; Nicholas M.

AB: Compositions and methods are provided for modulating the expression of protein kinase C. Oligonucleotides are provided which are targeted to nucleic acids encoding PKC.
The oligonucleotides are from 5 to 50 nucleotides in length and in one referred embodiment are from 12 to 18 nucleotides in length. The oligonucleotides may be chimeric oligonucleotides and in a preferred embodiment comprise at least one 2'-O-methoxyethyl modification. Pharmaceutical compositions comprising the oligonucleotides of the invention are also provided. Methods of inhibiting protein kinase C expression and methods of treating conditions associated with expression of protein kinase C using oligonucleotides of the invention are disclosed.

L7: Entry 11 of 42

File: USPT

Sep 12, 2000

DOCUMENT-IDENTIFIER: US 6117847 A
TITLE: Oligonucleotides for enhanced modulation of protein kinase C expression

BSPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides.
Penetration enhancers may be classified as belonging to one of five broad categories, ie., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8:91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7:1). One or more penetration enhancers from one or more of these broad categories may be included. Compositions comprising oligonucleotides and penetration enhancers are disclosed in co-pending U.S. patent application Ser. No. 08/886,829 to Teng et al., filed Jul. 1, 1997, which is herein incorporated by reference in its entirety.

12. Document ID: US 6114517 A

L7: Entry 12 of 42

File: USPT

Sep 5, 2000

US-PAT-NO: 6114517
DOCUMENT-IDENTIFIER: US 6114517 A
TITLE: Methods of modulating tumor necrosis factor .alpha.-induced expression of cell adhesion
molecules
DATE-ISSUED: September 5, 2000

US-CL-CURRENT: 536/24.5; 435/375, 435/6, 435/91.1, 435/91.31, 536/23.1, 536/24.3

APPL-NO: 9/ 209668
DATE FILED: December 10, 1998

IN: Monia; Brett P., Xu; Xiaoxing S.

AB: Methods are provided for inhibiting the expression of cell adhesion molecules
using inhibitors of signaling molecules involved in human TNF-.alpha. signaling. These
inhibitors include monoclonal antibodies, peptide fragments, small molecule inhibitors, and,
preferably, antisense oligonucleotides. Methods for treatment of diseases, particularly
inflammatory and immune diseases, associated with overexpression of cell adhesion molecules
are provided.

L7: Entry 12 of 42

File: USPT

Sep 5, 2000

DOCUMENT-IDENTIFIER: US 6114517 A
TITLE: Methods of modulating tumor necrosis factor .alpha.-induced expression of cell adhesion
molecules

DEPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may include
penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides.
Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty
acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical
Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi, Critical Reviews in
Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration enhancers from one or
more of these broad categories may be included.

13. Document ID: US 6111094 A

L7: Entry 13 of 42

File: USPT

Aug 29, 2000

US-PAT-NO: 6111094
DOCUMENT-IDENTIFIER: US 6111094 A
TITLE: Enhanced antisense modulation of ICAM-1
DATE-ISSUED: August 29, 2000

US-CL-CURRENT: 536/24.5; 435/375, 435/6, 536/24.31

APPL-NO: 9/ 062416
DATE FILED: April 17, 1998

PARENT-CASE:
CROSS-REFERENCES TO RELATED APPLICATIONS This application is a continuation-in-part of
application Ser. No. 08/440,740 (filed May 12, 1995, now U.S. Pat. No. 5,843,738), which is a
continuation-in-part of application Ser. No. 08/063,167 (filed May 17, 1993, now U.S. Pat. No.
5,514,788) which is a continuation of application Ser. No. 07/969,151 (filed Feb. 10, 1993, now
abandoned), which is a continuation-in-part of application Ser. No. 08/007,997 (filed Jan. 21,
1993, now U.S. Pat. No. 5,591,623), which is a continuation-in-part of application Ser. No.
07/939,855 (filed Sep. 2, 1992, now abandoned), which is a continuation-in-part of application
Ser. No. 07/567,286 (filed Aug. 14, 1990, now abandoned).

IN: Bennett; C. Frank, Condon; Thomas P., Flournoy; Shin Cheng

AB: The present invention provides compositions and methods for detecting and
modulating levels of intercellular adhesion molecule-1 (ICAM-1) proteins, including human
ICAM-1.

L7: Entry 13 of 42

File: USPT

Aug 29, 2000

DOCUMENT-IDENTIFIER: US 6111094 A
TITLE: Enhanced antisense modulation of ICAM-1

DEPR:
(1) Penetration Enhancers: Pharmaceutical compositions comprising the oligonucleotides of the
present invention may also include penetration enhancers in order to enhance the alimentary
delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of
five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and
non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991,
8:91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7:1).

14. Document ID: US 6100077 A

L7: Entry 14 of 42

File: USPT

Aug 8, 2000

US-PAT-NO: 6100077
DOCUMENT-IDENTIFIER: US 6100077 A
TITLE: Isolation of a gene encoding diacylglycerol acyltransferase
DATE-ISSUED: August 8, 2000

US-CL-CURRENT: 435/193; 435/183, 435/252.3, 435/254.2, 435/320.1, 435/325, 435/348, 435/410,
435/69.1, 536/23.1, 536/23.2

APPL-NO: 9/ 165042

DATE FILED: October 1, 1998

IN: Sturley; Stephen L., Oelkers; Peter

AB: This invention provides an isolated nucleic acid which encodes a diacylglycerol acyltransferase (DGAT); a vector comprising the isolated nucleic acid which encodes a diacylglycerol acyltransferase (DGAT); and a purified poly-peptide which is a diacylglycerol acyltransferase. This invention also provides an in vitro method of detecting a diacylglycerol acyltransferase binding site of an enzyme. This invention provides a method for determining whether a subject known to have an imbalance in trigliceride has the imbalance due to a defect in esterification of diacylglycerol to produce triglyceride. This invention also provides a method for treating a subject who has an imbalance in triglyceride levels due to a defect in esterification of diglycerol which comprises introducing the isolated nucleic acid which encodes a diacylglycerol acyltransferase (DGAT) into the subject under conditions such that the nucleic acid expresses a wildtype diacylglycerol acyltransferase, so as to thereby treat the subject. This invention further provides a method for inhibiting wildtype diacylglycerol acyltransferase in a subject which comprises transforming appropriate cells from the subject with a vector which expresses the nucleic acid which encodes a diacylglycerol acyltransferase (DGAT).

L7: Entry 14 of 42

File: USPT

Aug 8, 2000

DOCUMENT-IDENTIFIER: US 6100077 A
TITLE: Isolation of a gene encoding diacylglycerol acyltransferase

DEPR:
The above-described ligands, oligonucleotides polypeptides, or antibodies which are determined to be potentially therapeutic can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents, for example, enough saline or glucose to make the solution isotonic, bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

15. Document ID: US 6096722 A

L7: Entry 15 of 42

File: USPT

Aug 1, 2000

US-PAT-NO: 6096722
DOCUMENT-IDENTIFIER: US 6096722 A
TITLE: Antisense modulation of cell adhesion molecule expression and treatment of cell adhesion molecule-associated diseases
DATE-ISSUED: August 1, 2000

US-CL-CURRENT: 514/44; 435/325, 435/375, 435/6, 435/91.1, 536/23.1, 536/24.5

APPL-NO: 9/ 085759
DATE FILED: May 27, 1998

PARENT-CASE:
CROSS-REFERENCES TO RELATED APPLICATIONS This application is a continuation-in-part of application Ser. No. 08/440,740 (filed May 12, 1995, now U.S. Pat. No. 5,843,738), which is a continuation-in-part of application Ser. No. 08/063,167 (filed May 17, 1993, now U.S. Pat. No. 5,514,788) which is a continuation of application Ser. No. 07/969,151 (filed Feb. 10, 1993), now abandoned, which is a continuation-in-part of application Ser. No. 08/007,997 (filed Jan. 21, 1993, now U.S. Pat. No. 5,591,623), which is a continuation-in-part of application Ser. No. 07/939,855 (filed Sep. 2, 1992), now abandoned, which is a continuation-in-part of application Ser. No. 07/567,286 (filed Aug. 14, 1990), now abandoned. The contents of all of the aforementioned are herein incorporated by reference in their entirety.

IN: Bennett; C. Frank, Mirabelli; Christopher K., Baker; Brenda

AB: Compositions and methods are provided for the modulation of expression of cellular adhesion molecules. In accordance with preferred embodiments, oligonucleotides are provided which are specifically hybridizable with nucleic acids encoding intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and endothelial leukocyte adhesion molecule-1. Methods of modulating expression of cellular adhesion molecules are provided, as are methods of treating conditions associated with cellular adhesion molecules. In a preferred embodiment, the cellular adhesion molecule is ICAM-1, and a preferred antisense sequence targeted to human ICAM-1 is demonstrated to have clinical utility in several disease indications.

L7: Entry 15 of 42

File: USPT

Aug 1, 2000

DOCUMENT-IDENTIFIER: US 6096722 A
TITLE: Antisense modulation of cell adhesion molecule expression and treatment of cell adhesion molecule-associated diseases

DRPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems 1991, 8, 91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems 1990, 7, 1-33). One or more penetration enhancers from one or more of these broad categories may be included. Various fatty acids and their derivatives which act as penetration enhancers include, for example, oleic acid, lauric acid, capric acid, myristic acid, palmitic acid, stearic acid, linoleic acid, linolenic acid, dicaprate, tricaprate, recinleate, monoolein (a.k.a. 1-monooleoyl-rac-glycerol), dilaurin, caprylic acid, arachidonic

acid, glyceryl 1-monocaprate, 1-dodecylazacycloheptan-2-one, acylcarnitines, acylcholines, mono-
and di-glycerides and physiologically acceptable salts thereof (i.e., oleate, laurate, caprate,
myristate, palmitate, stearate, linoleate, etc.) (Lee et al., Critical Reviews in Therapeutic
Drug Carrier Systems 1991, page 92; Muranishi, Critical Reviews in Therapeutic Drug Carrier
Systems 1990, 7, 1; El-Hariri et al., J. Pharm. Pharmacol. 1992 44, 651-654). Sodium caprate and
sodium laurate are presently preferred, particularly in combination with one or more bile salts.

DEPR:
When a control solution of ISIS 2302 was administered no significant amount of oligonucleotides
was found to be absorbed at steady state. In contrast, when ISIS 2302 was formulated as a
solution that contained a mixture of fatty acid and bile salts (Formulations 1a and 1b) a
significant amount of oligonucleotide was found to be absorbed and bioavailable in the systemic
circulation. The absolute bioavailability of ISIS 2302 was found to be 14.6% from Formulation 1a
(containing a mixture of CDCA and fatty acid penetration enhancers) and 12.4% from Formulation 1b
(containing a mixture of UDCA and fatty acid penetration enhancers). The simple emulsion,
Formulation 1c, that is devoid of any penetration enhancers was also effective in making a
significant portion of the ISIS 2302 oligonucleotide bioavailable (absolute bioavailability of
20.4%).

16. Document ID: US 6087489 A

L7: Entry 16 of 42
File: USPT
Jul 11, 2000

US-PAT-NO: 6087489
DOCUMENT-IDENTIFIER: US 6087489 A
TITLE: Antisense oligonucleotide modulation of human thymidylate synthase expression
DATE-ISSUED: July 11, 2000

US-CL-CURRENT: 536/24.5; 435/325, 435/366, 435/6, 536/23.1

APPL-NO: 9/089195
DATE FILED: June 2, 1998

IN: Dean; Nicholas M.

AB: Compounds, compositions and methods are provided for modulating the expression of
human thymidylate synthase. The compositions comprise antisense oligonucleotides targeted to
nucleic acids encoding thymidylate synthase. Methods of using these oligonucleotides for
modulation of thymidylate synthase expression and for treatment of diseases such as cancers
believed to be responsive to modulation of thymidylate synthase expression are provided.

L7: Entry 16 of 42
File: USPT
Jul 11, 2000

DOCUMENT-IDENTIFIER: US 6087489 A
TITLE: Antisense oligonucleotide modulation of human thymidylate synthase expression

DEPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may include
penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides.
Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty
acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical
Reviews in Therapeutic Drug Carrier Systems 1991, 8, 91-192; Muranishi, Critical Reviews in
Therapeutic Drug Carrier Systems 1990, 7, 1-33). One or more penetration enhancers from one or
more of these broad categories may be included. Various fatty acids and their

17. Document ID: US 6080580 A

L7: Entry 17 of 42
File: USPT
Jun 27, 2000

US-PAT-NO: 6080580
DOCUMENT-IDENTIFIER: US 6080580 A
TITLE: Antisense oligonucleotide modulation of tumor necrosis factor-.alpha. (TNF-.alpha.)
expression
DATE-ISSUED: June 27, 2000

US-CL-CURRENT: 435/375; 435/366, 435/6, 435/91.1, 536/23.1, 536/24.31, 536/24.33, 536/24.5

APPL-NO: 9/166186
DATE FILED: October 5, 1998

IN: Baker; Brenda F., Bennett; C. Frank, Butler; Madeline M., Shanahan, Jr.; William
R.

AB: Compositions and methods are provided for inhibiting the expression of human
tumor necrosis factor-.alpha. (TNF-.alpha.). Antisense oligonucleotides targeted to nucleic
acids encoding TNF-.alpha. are preferred. Methods of using these oligonucleotides for
inhibition of TNF-.alpha. expression and for treatment of diseases, particularly
inflammatory and autoimmune diseases, associated with overexpression of TNF-.alpha. are
provided.

L7: Entry 17 of 42
File: USPT
Jun 27, 2000

DOCUMENT-IDENTIFIER: US 6080580 A
TITLE: Antisense oligonucleotide modulation of tumor necrosis factor-.alpha. (TNF-.alpha.)
expression

BSPR:
Pharmaceutical compositions comprising the oligonucleotides of the

present invention may include
penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides.
Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty
acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical
Reviews in Therapeutic Drug Carrier Systems 1991, 8, 91-192; Muranishi, Critical Reviews in
Therapeutic Drug Carrier Systems 1990, 7, 1-33). One or more penetration enhancers from one or
more of these broad categories may be included.

18. Document ID: US 6077672 A

L7: Entry 18 of 42
File: USPT
Jun 20, 2000

US-PAT-NO: 6077672
DOCUMENT-IDENTIFIER: US 6077672 A
TITLE: Antisense modulation of TRADD expression
DATE-ISSUED: June 20, 2000

US-CL-CURRENT: 435/6; 536/24.1, 536/24.5

APPL-NO: 9/ 143212
DATE FILED: August 28, 1998

IN: Monia; Brett P., Cowsert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the
expression of TRADD. The compositions comprise antisense compounds, particularly antisense
oligonucleotides, targeted to nucleic acids encoding TRADD. Methods of using these compounds
for modulation of TRADD expression and for treatment of diseases associated with expression
of TRADD are provided.

L7: Entry 18 of 42
File: USPT
Jun 20, 2000

DOCUMENT-IDENTIFIER: US 6077672 A
TITLE: Antisense modulation of TRADD expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present
invention may also include penetration enhancers in order to enhance the alimentary delivery of
the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad
categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee
et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi,
Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration
enhancers from one or more of these broad categories may be included. Penetration enhancers are
described in pending U.S. patent application Ser. No. 08/886,829, filed on Jul. 1, 1997, and
pending U.S. patent application Ser. No. 08/961,469, filed on Oct. 31, 1997, both of which are
commonly owned with the instant application and both of which are herein incorporated by
reference.

19. Document ID: US 6077709 A

L7: Entry 19 of 42
File: USPT
Jun 20, 2000

US-PAT-NO: 6077709
DOCUMENT-IDENTIFIER: US 6077709 A
TITLE: Antisense modulation of Survivin expression
DATE-ISSUED: June 20, 2000

US-CL-CURRENT: 435/375; 435/377, 435/455, 435/6, 536/23.1, 536/24.1, 536/24.5

APPL-NO: 9/ 163162
DATE FILED: September 29, 1998

IN: Bennett; C. Frank, Ackermann; Elizabeth J., Swayze; Eric E., Cowsert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the
expression of Survivin. The compositions comprise antisense compounds, particularly
antisense oligonucleotides, targeted to nucleic acids encoding Survivin. Methods of using
these compounds for modulation of Survivin expression and for treatment of diseases
associated with expression of Survivin are provided.

L7: Entry 19 of 42
File: USPT
Jun 20, 2000

DOCUMENT-IDENTIFIER: US 6077709 A
TITLE: Antisense modulation of Survivin expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present
invention may also include penetration enhancers in order to enhance the alimentary delivery of
the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad
categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee
et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi,
Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration
enhancers from one or more of these broad categories may be included. Penetration enhancers are
described in pending U.S. patent application Ser. No. 08/886,829, filed on Jul. 1, 1997, and
pending U.S. patent application Ser. No. 08/961,469, filed on Oct. 31, 1997, both of which are
commonly owned with the instant application and both of which are herein incorporated by
reference.

20. Document ID: US 6036953 A

L7: Entry 20 of 42

File: USPT

Mar 14, 2000

US-PAT-NO: 6036953
DOCUMENT-IDENTIFIER: US 6036953 A
TITLE: Heterologous antigens in live cell V. cholerae strains
DATE-ISSUED: March 14, 2000

US-CL-CURRENT: 424/93.2; 424/192.1, 424/234.1, 424/236.1, 424/239.1, 424/247.1, 424/261.1, 424/9.34, 424/93.1, 424/93.4 , 424/93.41, 514/837

APPL-NO: 8/ 977577
DATE FILED: November 25, 1997

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATION This application claims priority under 35 U.S.C. .sctn.119 from provisional application U.S. Ser. No. 60/032,328, filed Nov. 29, 1996.

IN: Ryan; Edward T., Calderwood; Stephen B.

AB: Disclosed is a V. cholerae cell containing a DNA encoding a fusion polypeptide that includes a heterologous antigenic polypeptide sequence such as a portion of C. difficile toxin A. The fusion polypeptide also includes one of the following: (i) an E. coli hemolysin A subunit (wich is coexpressed with sequences encoding hemolysin B and D subunits); (ii) a secretion signal sequence and cholera toxin A2 subunit (which is coexpressed with cholera toxin B subunit); or (iii) cholera toxin B subunit.

L7: Entry 20 of 42

File: USPT

Mar 14, 2000

DOCUMENT-IDENTIFIER: US 6036953 A
TITLE: Heterologous antigens in live cell V. cholerae strains

DEPR:
To judge intestinal colonization of V. cholerae 0395-NT (pETR14) and plasmid retention, a separate cohort of rabbits was orally inoculated once. Washed ilea from these rabbits were quantitatively examined for the presence of pETR14 on serial days as previously described (Cray et al., Infect. Immun., 1983, 41:735-741; Pierce et al., Infect. Immun., 1988, 56:142-148; Pierce et al., Infect. Immun., 1985, 813-816). Rabbits were inoculated as described above with 10.sup.10 cfu of 0395-NT (pETR14). The plasmid pETR14 contains an ampicillin resistance gene. Four rabbits received normal water and two rabbits received water containing ampicillin (1 mg/ml). Beginning on day 2, rabbits were appropriately anesthetized and then sacrificed with Fatal-Plus (Vortech Pharmaceuticals, Dearborn, Mich.) on serial days. A 10 cm segment of ileum (beginning 10 cm proximal to the mesoappendix and moving cephalad) was removed, opened, washed in PBS, weighed, and homogenized (Tissue Grinder, Corning Inc., Corning, N.Y.) in LB. The removed ileum was then quantitatively cultured on LB medium containing streptomycin (Cray et al., Infect. Immun., 1983, 41:735-741; Pierce et al., Infect. Immun., 1988, 56:142-148; Pierce et al., Infect. Immun., 1985, 813-816). After overnight incubation, colonies were replica-plated on thiosulfate-citrate-bile salts-sucrose plates and on LB medium containing ampicillin. DNA from representative colonies growing on LB medium containing ampicillin was isolated in order to confirm the presence of pETR14.

21. Document ID: US 6030786 A

L7: Entry 21 of 42

File: USPT

Feb 29, 2000

US-PAT-NO: 6030786
DOCUMENT-IDENTIFIER: US 6030786 A
TITLE: Antisense modulation of RhoC expression
DATE-ISSUED: February 29, 2000

US-CL-CURRENT: 435/6; 435/325, 435/366, 435/91.1, 536/23.1, 536/24.31, 536/24.5

APPL-NO: 9/ 156807
DATE FILED: September 18, 1998

IN: Cowsert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the expression of RhoC. The compositions comprise antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding RhoC. Methods of using these compounds for modulation of RhoC expression and for treatment of diseases associated with expression of RhoC are provided.

L7: Entry 21 of 42

File: USPT

Feb 29, 2000

DOCUMENT-IDENTIFIER: US 6030786 A
TITLE: Antisense modulation of RhoC expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration enhancers from one or more of these broad categories may be included. Penetration enhancers are described in pending U.S. patent application Ser. No. 08/886,829, filed on Jul. 1, 1997, and pending U.S. patent application Ser. No. 08/961,469, filed on Oct. 31, 1997, United States patent X,XXX,XXX, both of which are commonly owned with the instant application and both of which are

herein incorporated by reference.

22. Document ID: US 6022737 A

L7: Entry 22 of 42

File: USPT

Feb 8, 2000

US-PAT-NO: 6022737
DOCUMENT-IDENTIFIER: US 6022737 A
TITLE: Formulations for non-viral in vivo transfection in the lungs
DATE-ISSUED: February 8, 2000

US-CL-CURRENT: 435/320.1; 424/93.21, 435/325, 435/455, 435/69.1, 514/44

APPL-NO: 8/ 556780
DATE FILED: November 2, 1995

IN: Niven; Ralph, Freeman; Daniel J.

AB: Formulations useful in improving non-viral in vivo transfection of DNA in the lungs are provided. Formulations which comprise DNA with various additives are prepared and delivered to the lungs resulting in production of a transcription product.

L7: Entry 22 of 42

File: USPT

Feb 8, 2000

DOCUMENT-IDENTIFIER: US 6022737 A
TITLE: Formulations for non-viral in vivo transfection in the lungs

DEPR:
In one aspect of the invention, the additive is a permeation enhancer. Permeation enhancers which may be employed include bile salts such as sodium glycocholate and other molecules such as .beta.-cyclodextrin. Bile salts are known to increase the absorption of macromolecules across membranes; Pontiroli et al., Diabet. Metab., 13:441-43 (1987) and also act as protease inhibitors; Morita et al., Pharm. Res., 11:909-13 (1994). Molecules such as .beta.-cyclodextrin have been used primarily as "solublizing" agents for drugs of low aqueous solubility; Brewster et al., Pharm. Res., 8:792-795 (1991) and have also been found to enhance uptake of albuterol from the lungs; Marques et al., Int. J. Pharm., 77:303-307 (1991). In a particularly preferred embodiment, the transfection agent comprises plasmid DNA and the additive, sodium glycocholate.

23. Document ID: US 6020198 A

L7: Entry 23 of 42

File: USPT

Feb 1, 2000

US-PAT-NO: 6020198
DOCUMENT-IDENTIFIER: US 6020198 A
TITLE: Antisense modulation of RIP-1 expression
DATE-ISSUED: February 1, 2000

US-CL-CURRENT: 435/375; 435/6, 536/23.1, 536/24.1, 536/24.5

APPL-NO: 9/ 161443
DATE FILED: September 25, 1998

IN: Bennett; C. Frank, Cowsert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the expression of RIP-1. The compositions comprise antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding RIP-1. Methods of using these compounds for modulation of RIP-1 expression and for treatment of diseases associated with expression of RIP-1 are provided.

L7: Entry 23 of 42

File: USPT

Feb 1, 2000

DOCUMENT-IDENTIFIER: US 6020198 A
TITLE: Antisense modulation of RIP-1 expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration enhancers from one or more of these broad categories may be included. Penetration enhancers are described in pending U.S. patent application Ser. No. 08/886,829, filed on Jul. 1, 1997, and pending U.S. patent application Ser. No. 08/961,469, filed on Oct. 31, 1997, both of which are commonly owned with the instant application and both of which are herein incorporated by reference.

24. Document ID: US 6013500 A

L7: Entry 24 of 42

File: USPT

Jan 11, 2000

US-PAT-NO: 6013500
DOCUMENT-IDENTIFIER: US 6013500 A
TITLE: PAK4, a novel gene encoding a serine/threonine kinase
DATE-ISSUED: January 11, 2000

US-CL-CURRENT: 435/194; 435/252.3, 435/320.1, 435/325

APPL-NO: 9/ 082737
DATE FILED: May 21, 1998

IN: Minden; Audrey

AB: This invention provides an isolated mammalian nucleic acid molecule encoding a PAK4 serine/threonine kinase. This invention provides an isolated nucleic acid molecule encoding a mutant homolog of the mammalian PAK4 serine/threonine kinase whose amino acid sequence is set forth in FIG. 1A (SEQ ID NO: 2). This invention provides a fusion protein comprising a PAK4 serine/threonine kinase or a fragment thereof and a second peptide. This invention provides a purified mammalian PAK4 serine/threonine kinase. This invention provides a protein comprising substantially the amino acid sequence set forth in FIG. 1A. This invention provides a monoclonal antibody directed to an epitope of a PAK4 serine/threonine kinase. This invention provides a method of inhibiting PAK4 function comprising administering a ligand comprising an amino acid domain which binds to a GTP binding protein so as to inhibit binding of the GTP binding protein to PAK4. This invention provides a method of inhibiting PAK4 function comprising administering a ligand which binds to the GTP binding domain of PAK4 so as to inhibit PAK4 binding to a GTP binding protein. This invention provides a method of inhibiting PAK4 serine/threonine kinase function comprising administering a ligand which blocks an ATP binding domain so as to inhibit PAK4 serine/threonine kinase function. This invention provides a method of inhibiting growth of a tumor cell comprising blocking Cdc42Hs by administering a ligand capable of binding to a Cdc42Hs binding site of a PAK4 serine/threonine kinase.

L7: Entry 24 of 42

File: USPT

Jan 11, 2000

DOCUMENT-IDENTIFIER: US 6013500 A
TITLE: PAK4, a novel gene encoding a serine/threonine kinase

DEPR: The above-described ligands, oligonucleotides or antibodies which are determined to be potentially therapeutic can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents, for example, enough saline or glucose to make the solution isotonic, bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

25. Document ID: US 6007991 A

L7: Entry 25 of 42

File: USPT

Dec 28, 1999

US-PAT-NO: 6007991
DOCUMENT-IDENTIFIER: US 6007991 A
TITLE: Antisense oligonucleotides for mitogen-activated protein kinases as therapy for cancer

DATE-ISSUED: December 28, 1999

US-CL-CURRENT: 435/6; 435/325, 514/44, 536/24.5

APPL-NO: 8/ 909742
DATE FILED: August 12, 1997

PARENT-CASE:
This application is a continuation-in-part of U.S. Ser. No. 08/831,994, filed on Apr. 1, 1997, now abandoned, which is a continuation-in-part of U.S. Ser. No. 08/827,520, filed on Mar. 28, 1997, now abandoned.

IN: Sivaraman; Vimala S., Wang; Hsien-yu, Malbon; Craig C.

AB: A method is disclosed for inhibiting malignant neoplastic growth of epithelial or endothelial cells in a mammal by administering to the mammal an effective amount of an oligonucleotide complementary to at least a portion of mRNA for ERK-1 or ERK-2 that is overexpressed in the mammal. The antisense oligonucleotides are administered to the mammal as a dosage unit. A method of identifying and monitoring potentially malignant neoplastic cell growth in a mammal is also disclosed.

L7: Entry 25 of 42

File: USPT

Dec 28, 1999

DOCUMENT-IDENTIFIER: US 6007991 A
TITLE: Antisense oligonucleotides for mitogen-activated protein kinases as therapy for cancer

DEPR: The oligonucleotides of the invention may also be administered by any method known in the art for systemic administration. Some suitable methods for systemic administration include, for example, transmucosal, transdermal, or oral methods. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated may be used in the formulation. Such penetrants are generally known in the art, and include, for example, bile salts and fusidic acid derivatives for transmucosal administration. In addition, enhancers can be used to facilitate permeation. Transmucosal administration can be through use of nasal sprays, for example, or suppositories. For oral administration, the oligonucleotides are formulated into conventional oral administration forms such as capsules, tablets, and tonics.

26. Document ID: US 6007995 A

L7: Entry 26 of 42

File: USPT

Dec 28, 1999

US-PAT-NO: 6007995
DOCUMENT-IDENTIFIER: US 6007995 A
TITLE: Antisense inhibition of TNFR1 expression
DATE-ISSUED: December 28, 1999

US-CL-CURRENT: 435/6; 435/325, 435/366, 435/377, 435/91.1,

536/23.1, 536/24.31, 536/24.5

APPL-NO: 9/ 106038
DATE FILED: June 26, 1998

IN: Baker; Brenda F., Cowsert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the
expression of TNFR1. The compositions comprise antisense compounds, particularly antisense
oligonucleotides, targeted to nucleic acids encoding TNFR1. Methods of using these compounds
for modulation of TNFR1 expression and for treatment of diseases associated with expression
of TNFR1 are provided.

L7: Entry 26 of 42
File: USPT
Dec 28, 1999

DOCUMENT-IDENTIFIER: US 6007995 A
TITLE: Antisense inhibition of TNFR1 expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present
invention may also include penetration enhancers in order to enhance the alimentary delivery of
the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad
categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee
et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi,
Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration
enhancers from one or more of these broad categories may be included. Penetration enhancers are
described in pending U.S. patent application Ser. No. 08/886,829, filed on Jul. 1, 1997, U.S.
Pat. No. X,XXX,XXX, and pending U.S. patent application Ser. No. 08/961,469, filed on Oct. 31,
1997, U.S. Pat. No. X,XXX,XXX, both of which are commonly owned with the instant application and
both of which are herein incorporated by reference.

27. Document ID: US 6004814 A

L7: Entry 27 of 42
File: USPT
Dec 21, 1999

US-PAT-NO: 6004814
DOCUMENT-IDENTIFIER: US 6004814 A
TITLE: Antisense modulation of CD71 expression
DATE-ISSUED: December 21, 1999

US-CL-CURRENT: 435/375; 435/6, 536/23.1, 536/24.1, 536/24.5

APPL-NO: 9/ 161244
DATE FILED: September 25, 1998

IN: Bennett; C. Frank, Cowsert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the
expression of CD71. The compositions comprise antisense compounds, particularly antisense
oligonucleotides, targeted to nucleic acids encoding CD71. Methods of using these compounds
for modulation of CD71 expression and for treatment of diseases associated with expression
of CD71 are provided.

L7: Entry 27 of 42
File: USPT
Dec 21, 1999

DOCUMENT-IDENTIFIER: US 6004814 A
TITLE: Antisense modulation of CD71 expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present
invention may also include penetration enhancers in order to enhance the alimentary delivery of
the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad
categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee
et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi,
Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration
enhancers from one or more of these broad categories may be included. Penetration enhancers are
described in pending U.S. patent application Ser. No. 08/886,829, filed on Jul. 1, 1997, and
pending U.S. patent application Ser. No. 08/961,469, filed on Oct. 31, 1997, both of which are
commonly owned with the instant application and both of which are herein incorporated by
reference.

28. Document ID: US 6001652 A

L7: Entry 28 of 42
File: USPT
Dec 14, 1999

US-PAT-NO: 6001652
DOCUMENT-IDENTIFIER: US 6001652 A
TITLE: Antisense modulation of cREL expression
DATE-ISSUED: December 14, 1999

US-CL-CURRENT: 435/375; 435/369, 435/371, 435/6, 435/91.1, 536/23.1, 536/24.31, 536/24.5

APPL-NO: 9/ 156253
DATE FILED: September 18, 1998

IN: Monia; Brett P., Baker; Brenda F., Cowsert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the
expression of cREL. The compositions comprise antisense compounds, particularly antisense
oligonucleotides, targeted to nucleic acids encoding cREL. Methods of using these compounds
for modulation of cREL expression and for treatment of diseases associated with expression
of cREL are provided.

L7: Entry 28 of 42

File: USPT

Dec 14, 1999

DOCUMENT-IDENTIFIER: US 6001652 A
TITLE: Antisense modulation of cREL expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration enhancers from one or more of these broad categories may be included. Penetration enhancers are described in pending U.S. patent application Ser. No. 08/886,829, filed on Jul. 1, 1997, and pending U.S. patent application Ser. No. 08/961,469, filed on Oct. 31, 1997, both of which are commonly owned with the instant application and both of which are herein incorporated by reference.

29. Document ID: US 6001651 A

L7: Entry 29 of 42

File: USPT

Dec 14, 1999

US-PAT-NO: 6001651
DOCUMENT-IDENTIFIER: US 6001651 A
TITLE: Antisense modulation of LFA-3
DATE-ISSUED: December 14, 1999

US-CL-CURRENT: 435/375; 435/371, 435/6, 435/91.1, 536/23.1, 536/24.31, 536/24.33, 536/24.5

APPL-NO: 9/045106
DATE FILED: March 20, 1998

IN: Bennett; C. Frank, Condon; Thomas P., Flournoy; Shin Cheng, Pober; Jordan S., Ma; Weillie

AB: Compositions and methods for the treatment and diagnosis of diseases or disorders amenable to treatment through modulation of expression of a nucleic acid encoding a lymphocyte function associated antigen 3 (LFA-3; also known as CD58) protein are provided.

L7: Entry 29 of 42

File: USPT

Dec 14, 1999

DOCUMENT-IDENTIFIER: US 6001651 A
TITLE: Antisense modulation of LFA-3

DEPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8:91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7:1).

30. Document ID: US 6001992 A

L7: Entry 30 of 42

File: USPT

Dec 14, 1999

US-PAT-NO: 6001992
DOCUMENT-IDENTIFIER: US 6001992 A
TITLE: Antisense modulation of novel anti-apoptotic bcl-2-related proteins
DATE-ISSUED: December 14, 1999

US-CL-CURRENT: 536/24.5; 435/375, 435/440, 435/6, 435/91.1, 536/23.1, 536/24.3

APPL-NO: 9/226568
DATE FILED: January 7, 1999

IN: Ackermann; Elizabeth J., Bennett; C. Frank, Dean; Nicholas M., Marcusson; Eric G.

AB: Compositions and methods are provided for modulating the expression of novel anti-apoptotic bcl-2-related proteins. Antisense oligonucleotides targeted to nucleic acids encoding the human novel anti-apoptotic bcl-2-related proteins A1 and mcl-1 are preferred. Methods of using these compounds for modulation of novel anti-apoptotic bcl-2-related protein expression and for treatment of diseases associated with expression of novel anti-apoptotic bcl-2-related proteins are also provided. Also provided are methods of using these compounds for promoting apoptosis and for treatment of diseases for which promotion of apoptosis is desired.

L7: Entry 30 of 42

File: USPT

Dec 14, 1999

DOCUMENT-IDENTIFIER: US 6001992 A
TITLE: Antisense modulation of novel anti-apoptotic bcl-2-related proteins

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi,

Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration
enhancers from one or more of these broad categories may be included.

31. Document ID: US 5998596 A

L7: Entry 31 of 42

File: USPT

Dec 7, 1999

US-PAT-NO: 5998596
DOCUMENT-IDENTIFIER: US 5998596 A
TITLE: Inhibition of protein kinase activity by aptameric action of oligonucleotides
DATE-ISSUED: December 7, 1999

US-CL-CURRENT: 536/22.1; 536/23.1, 536/24.3

APPL-NO: 8/ 416214
DATE FILED: April 4, 1995

IN: Bergan; Raymond, Neckers; Len

AB: The present invention are oligonucleotides that specifically bind to and directly
inhibit the biological function of target molecules such as proteins, peptides or
derivatives. The direct or aptameric interaction of oligonucleotides of the present
invention with proteins, peptides and derivatives represents a non-antisense mediated
effect. The oligonucleotides have been shown to bind to isolated target molecules and to
inhibit biological function of the target molecule within cells. In particular, the
oligonucleotides have been shown to directly inhibit the kinase activity of protein-tyrosine
kinase. The oligonucleotides of the present invention have significant beneficial effects
against a chronic myelogenous leukemia derived cell line as demonstrated using cellular
phosphotyrosine content as well as cellular growth in soft agar.

L7: Entry 31 of 42

File: USPT

Dec 7, 1999

DOCUMENT-IDENTIFIER: US 5998596 A
TITLE: Inhibition of protein kinase activity by aptameric action of oligonucleotides

DEPR:
Administration may also be by transmucosal or transdermal means, or the compounds may be
administered orally. For transmucosal or transdermal administration, penetrants appropriate to
the barrier to be permeated as used in the formulation. Such penetrants are generally known in
the art, and include, for example, for transmucosal administration bile salts and fusidic acid
derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal
administration may be through nasal sprays, for example, or using suppositories. For oral
administration, the oligonucleotides are formulated into conventional oral administration forms
such as capsules, tablets, and tonics.

32. Document ID: US 5994062 A

L7: Entry 32 of 42

File: USPT

Nov 30, 1999

US-PAT-NO: 5994062
DOCUMENT-IDENTIFIER: US 5994062 A
TITLE: Epithelial protein and DNA thereof for use in early cancer detection
DATE-ISSUED: November 30, 1999

US-CL-CURRENT: 435/6; 435/91.2, 435/91.21, 536/23.5, 536/24.32, 536/24.33

APPL-NO: 8/ 538711
DATE FILED: October 2, 1995

IN: Mulshine; James L., Tockman; Melvyn S.

AB: The present invention is a purified and isolated epithelial protein, peptide and
variants thereof whose increased presence in an epithelial cell is at indicative of
precancer. One epithelial protein which is an early detection marked for lung cancer was
purified from two human lung cancer cell lines, NCI-H720 and NCI-H157. Using a six-step
procedure, the epithelial protein was purified using a Western blot detection system under
both non-reducing and reducing conditions. Purification steps included anion exchange
chromatography, preparative isoelectric focusing, polymer-based C.sub.18 HPLC and analytic
C.sub.4 HPLC. After an approximately 25,000 fold purification the immunostaining protein was
>90% pure as judged by coomassie blue staining after reducing SDS-PAGE. The primary
epithelial protein share some sequence homology with the heterogeneous nuclear
ribonucleoprotein (hnRNP) A2. A minor co-purifying epithelial protein shares some sequence
homology with the splice variant hnRNP-B1. Molecular analysis of primary nonnal bronchial
epithelial cell cultures demonstrated a low level the epithelial protein expression,
consistent with immunohistochemical staining of clinical samples, and an increased level of
expression in most lung cancer cells. The epithelial protein is a marker of epithelial
transformation in lung, breast, bone, ovary, prostate, kidney, melanoma and myeloma and may
be casual in the process of carcinogenesis. Methods are provided for monitoring the
expression of the epithelial protein, peptides and variants using molecular and
immunological techniques as a screen for precancer and cancer in mammals.

L7: Entry 32 of 42

File: USPT

Nov 30, 1999

DOCUMENT-IDENTIFIER: US 5994062 A
TITLE: Epithelial protein and DNA thereof for use in early cancer detection

DEPR:
The route of administration may be intravenous, intramuscular, subcutaneous, intradermal,
intraperitoneal, intrathecal, ex vivo, and the like. Administration may also be by transmucosal
or transdermal means, or the compound may be administered orally. For transmucosal or transdermal
administration, penetrants appropriate to the barrier to be permeated as used in the formulation.
Such penetrants are generally known in the art, and include, for example, for transmucosal
administration bile salts and fusidic acid derivatives. In addition, detergents may be used to
facilitate permeation. Transmucosal administration may be through nasal sprays, for example, or
using suppositories. For oral administration, the oligonucleotides are formulated into
conventional oral administration forms, such as capsules, tablets and tonics. For topical
administration, the oligonucleotides of the invention are formulated into ointments, salves,
gels, or creams, as is generally known in the art.

33. Document ID: US 5968826 A

L7: Entry 33 of 42
File: USPT
Oct 19, 1999

US-PAT-NO: 5968826
DOCUMENT-IDENTIFIER: US 5968826 A
TITLE: Antisense inhibition of integrin .alpha.4 expression
DATE-ISSUED: October 19, 1999

US-CL-CURRENT: 435/375; 435/325, 435/366, 435/6, 435/91.1, 536/23.1, 536/24.31, 536/24.33,
536/24.5

APPL-NO: 9/ 166203
DATE FILED: October 5, 1998

IN: Bennett; C. Frank, Condon; Thomas P., Cowsert; Lex M.

AB: Compositions and methods are provided for modulating the expression of integrin
.alpha.4. Antisense compounds, particularly antisense oligonucleotides, targeted to nucleic
acids encoding integrin .alpha.4 are preferred. Methods of using these compounds for
modulating integrin .alpha.4 expression and for treatment of diseases associated with
expression of integrin .alpha.4 are also provided.

L7: Entry 33 of 42
File: USPT
Oct 19, 1999

DOCUMENT-IDENTIFIER: US 5968826 A
TITLE: Antisense inhibition of integrin .alpha.4 expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present
invention may also include penetration enhancers in order to enhance the alimentary delivery of
the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad
categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee
et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi,
Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration
enhancers from one or more of these broad categories may be included. Penetration enhancers are
described in pending U.S. patent application Ser. No. 08/886,829, filed on Jul. 1, 1997, and
pending U.S. patent application Ser. No. 08/961,469, filed on Oct. 31, 1997, both of which are
commonly owned with the instant application and both of which are herein incorporated by
reference.

34. Document ID: US 5968748 A

L7: Entry 34 of 42
File: USPT
Oct 19, 1999

US-PAT-NO: 5968748
DOCUMENT-IDENTIFIER: US 5968748 A
TITLE: Antisense oligonucleotide modulation of human HER-2 expression
DATE-ISSUED: October 19, 1999

US-CL-CURRENT: 435/6; 435/325, 435/366, 435/375, 435/91.1, 536/23.1, 536/24.31, 536/24.5

APPL-NO: 9/ 048804
DATE FILED: March 26, 1998

IN: Bennett; C. Frank, Lipton; Allan, Witters; Lois M.

AB: Compounds, compositions and methods are provided for inhibiting the expression of
human HER-2 (also known as c-neu, ErbB-2 and HER-2/neu). The compositions comprise antisense
oligonucleoptides targeted to nucleic acids encoding HER-2. Methods of using these
oligonucleotides for inhibition of HER-2 expression and for treatment of diseases such as
cancers associated with overexpression of HER-2 are provided. Methods of inhibiting other
growth factor receptors using antisense oligonucleotides targeted to nucleic acids encoding
HER-2 are also provided.

L7: Entry 34 of 42
File: USPT
Oct 19, 1999

DOCUMENT-IDENTIFIER: US 5968748 A
TITLE: Antisense oligonucleotide modulation of human HER-2 expression

BSPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may include
penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides.
Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty
acids, bile salts, chelating agents, surfactants and non-surfactants. Lee, et al., Critical
Reviews in Therapeutic Drug Carrier Systems, 1991, 8:91-192 and Muranishi, Critical Reviews in

Therapeutic Drug Carrier Systems, 1990, 7, 1. One or more penetration enhancers from one or more
of these broad categories may be included. Compositions comprising oligonucleotides and
penetration enhancers are disclosed in co-pending U.S. patent application Ser. No. 08/886,829 to
Teng, et al., filed Jul. 1, 1997, which is incorporated herein by reference in its entirety.

35. Document ID: US 5965370 A

L7: Entry 35 of 42

File: USPT

Oct 12, 1999

US-PAT-NO: 5965370
DOCUMENT-IDENTIFIER: US 5965370 A
TITLE: Antisense modulation of RhoG expression
DATE-ISSUED: October 12, 1999

US-CL-CURRENT: 435/6; 435/325, 435/366, 435/375, 435/91.1, 536/23.1, 536/24.31, 536/24.5

APPL-NO: 9/ 161015
DATE FILED: September 25, 1998

IN: Cowsert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the
expression of RhoG. The compositions comprise antisense compounds, particularly antisense
oligonucleotides, targeted to nucleic acids encoding RhoG. Methods of using these compounds
for modulation of RhoG expression and for treatment of diseases associated with expression
of RhoG are provided.

L7: Entry 35 of 42

File: USPT

Oct 12, 1999

DOCUMENT-IDENTIFIER: US 5965370 A
TITLE: Antisense modulation of RhoG expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present
invention may also include penetration enhancers in order to enhance the alimentary delivery of
the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad
categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee
et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi,
Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration
enhancers from one or more of these broad categories may be included. Penetration enhancers are
described in pending U.S. patent application 08/886,829, filed on Jul. 1, 1997, and pending U.S.
patent application 08/961,469, filed on Oct. 31, 1997, both of which are commonly owned with the
instant application and both of which are herein incorporated by reference.

36. Document ID: US 5962671 A

L7: Entry 36 of 42

File: USPT

Oct 5, 1999

US-PAT-NO: 5962671
DOCUMENT-IDENTIFIER: US 5962671 A
TITLE: Antisense modulation of fan expression
DATE-ISSUED: October 5, 1999

US-CL-CURRENT: 536/24.5; 435/375, 536/23.1, 536/24.1, 536/24.3

APPL-NO: 9/ 156425
DATE FILED: September 18, 1998

IN: Baker; Brenda F., Cowsert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the
expression of FAN. The compositions comprise antisense compounds, particularly antisense
oligonucleotides, targeted to nucleic acids encoding FAN. Methods of using these compounds
for modulation of FAN expression and for treatment of diseases associated with expression of
FAN are provided.

L7: Entry 36 of 42

File: USPT

Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5962671 A
TITLE: Antisense modulation of fan expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present
invention may also include penetration enhancers in order to enhance the alimentary delivery of
the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad
categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee
et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi,
Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration
enhancers from one or more of these broad categories may be included. Penetration enhancers are
described in pending U.S. patent application Ser. No. 08/886,829, filed on Jul. 1, 1997, and
pending U.S. patent application Ser. No. 08/961,469, filed on Oct. 31, 1997, both of which are
commonly owned with the instant application and both of which are herein incorporated by
reference.

37. Document ID: US 5962672 A

L7: Entry 37 of 42

File: USPT

Oct 5, 1999

US-PAT-NO: 5962672
DOCUMENT-IDENTIFIER: US 5962672 A
TITLE: Antisense modulation of RhoB expression
DATE-ISSUED: October 5, 1999

US-CL-CURRENT: 536/24.5; 435/375, 536/23.1, 536/24.1, 536/24.3

APPL-NO: 9/ 156979
DATE FILED: September 18, 1998

IN: Coswert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the
expression of RhoB. The compositions comprise antisense compounds, particularly antisense
oligonucleotides, targeted to nucleic acids encoding RhoB. Methods of using these compounds
for modulation of RhoB expression and for treatment of diseases associated with expression
of RhoB are provided.

L7: Entry 37 of 42

File: USPT

Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5962672 A
TITLE: Antisense modulation of RhoB expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present
invention may also include penetration enhancers in order to enhance the alimentary delivery of
the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad
categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee
et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi,
Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration
enhancers from one or more of these broad categories may be included. Penetration enhancers are
described in pending U.S. patent application Ser. No. 08/886,829, filed on Jul. 1, 1997, and
pending U.S. patent application Ser. No. 08/961,469, filed on Oct. 31, 1997, both of which are
commonly owned with the instant application and both of which are herein incorporated by
reference.

38. Document ID: US 5955443 A

L7: Entry 38 of 42

File: USPT

Sep 21, 1999

US-PAT-NO: 5955443
DOCUMENT-IDENTIFIER: US 5955443 A
TITLE: Antisense modulation of PECAM-1
DATE-ISSUED: September 21, 1999

US-CL-CURRENT: 514/44; 435/375, 435/6, 435/91.1, 536/23.1, 536/24.31, 536/24.5

APPL-NO: 9/ 044506
DATE FILED: March 19, 1998

IN: Bennett; C. Frank, Condon; Thomas P., Flournoy; Shin Cheng, Zhang; Hong

AB: Compositions and methods for the treatment and diagnosis of diseases or disorders
amenable to treatment through modulation of expression of a nucleic acid encoding a platelet
endothelial cell adhesion molecule-1 (PECAM-1; also known as CD31 antigen or endoCAM)
protein are provided.

L7: Entry 38 of 42

File: USPT

Sep 21, 1999

DOCUMENT-IDENTIFIER: US 5955443 A
TITLE: Antisense modulation of PECAM-1

DEPR:
(1) Penetration Enhancers: Pharmaceutical compositions comprising the oligonucleotides of the
present invention may also include penetration enhancers in order to enhance the alimentary
delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of
five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and
non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991,
8:91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7:1).

39. Document ID: US 5945290 A

L7: Entry 39 of 42

File: USPT

Aug 31, 1999

US-PAT-NO: 5945290
DOCUMENT-IDENTIFIER: US 5945290 A
TITLE: Antisense modulation of RhoA expression
DATE-ISSUED: August 31, 1999

US-CL-CURRENT: 435/6; 435/325, 435/366, 435/91.1, 536/23.1, 536/24.5

APPL-NO: 9/ 156424
DATE FILED: September 18, 1998

IN: Cowsert; Lex M.

AB: Antisense compounds, compositions and methods are provided for modulating the
expression of RhoA. The compositions comprise antisense compounds, particularly antisense
oligonucleotides, targeted to nucleic acids encoding RhoA. Methods of using these compounds
for modulation of RhoA expression and for treatment of diseases associated with expression
of RhoA are provided.

L7: Entry 39 of 42

File: USPT

Aug 31, 1999

DOCUMENT-IDENTIFIER: US 5945290 A
TITLE: Antisense modulation of RhoA expression

BSPR:
Pharmaceutical compositions and/or formulations comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, 91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7, 1-33). One or more penetration enhancers from one or more of these broad categories may be included. Penetration enhancers are described in pending U.S. patent application Ser. No. 08/886,829, filed on Jul. 1, 1997, and pending U.S. patent application Ser. No. 08/961,469, filed on Oct. 31, 1997, both of which are commonly owned with the instant application and both of which are herein incorporated by reference.

40. Document ID: US 5877309 A

L7: Entry 40 of 42

File: USPT

Mar 2, 1999

US-PAT-NO: 5877309
DOCUMENT-IDENTIFIER: US 5877309 A
TITLE: Antisense oligonucleotides against JNK
DATE-ISSUED: March 2, 1999

US-CL-CURRENT: 536/24.5; 435/371, 435/375, 435/6, 435/91.1, 536/23.1, 536/24.3

APPL-NO: 8/ 910629
DATE FILED: August 13, 1997

IN: McKay; Robert, Dean; Nicholas M.

AB: Compositions and methods for the treatment and diagnosis of diseases or disorders amenable to treatment through modulation of expression of a gene encoding a Jun N-terminal kinase (JNK protein) are provided. Oligonucleotide are herein provided which are specifically hybridizable with nucleic acids encoding JNK1, JNK2 and JNK3, as well as other JNK proteins and specific isoforms thereof. Methods of treating animals suffering from diseases or disorders amenable to therapeutic intervention by modulating the expression of one or more JNK proteins with such oligonucleotide are also provided. Methods for the treatment and diagnosis of diseases or disorders associated with aberrant expression of one or more JNK proteins are also provided. The invention is thus directed to compositions for modulating, diagnostic methods for detecting, and therapeutic methods for inhibiting, the hyperproliferation of cells and formation, development and maintenance of tumors.

L7: Entry 40 of 42

File: USPT

Mar 2, 1999

DOCUMENT-IDENTIFIER: US 5877309 A
TITLE: Antisense oligonucleotides against JNK

DEPR:
Pharmaceutical compositions comprising the oligonucleotides of the present invention may also include penetration enhancers in order to enhance the alimentary delivery of the oligonucleotides. Penetration enhancers may be classified as belonging to one of five broad categories, i.e., fatty acids, bile salts, chelating agents, surfactants and non-surfactants (Lee et al., Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8:91-192; Muranishi, Critical Reviews in Therapeutic Drug Carrier Systems, 1990, 7:1).

41. Document ID: US 5534496 A

L7: Entry 41 of 42

File: USPT

Jul 9, 1996

US-PAT-NO: 5534496
DOCUMENT-IDENTIFIER: US 5534496 A
TITLE: Methods and compositions to enhance epithelial drug transport
DATE-ISSUED: July 9, 1996

US-CL-CURRENT: 514/17; 424/434, 514/18, 514/19, 530/330, 530/331

APPL-NO: 8/ 219156
DATE FILED: March 29, 1994

PARENT-CASE:
RELATED APPLICATION This application is a continuation-in-part application of prior application Ser. No. 07/909,908, filed on Jul. 7, 1992, now abandoned.

IN: Lee; Vincent H., Yen; Wan-Ching

AB: Methods and compositions provided for enhancing the transport of drugs (including peptides, oligonucleotides, proteins and conventional drugs) across epithelial cells at mucosal sites. The methods and compositions include the use of a peptide comprising at least two amino acids, such as Pro-Leu-Gly-Pro-Arg or Pro-Leu, and a protective group such as phenylazo-benzyloxycarbonyl, N-methyl, t-butyloxycarbonyl, fluorocnylmethyloxycarbonyl or carbobenzoxy, at the N-terminus, or in a mixture of such peptides in a sufficient amount to enhance the drug transport across epithelial cells at mucosal sites. Preferably, the peptide comprises 2 to 5 amino acids; the N-terminal amino acids are preferably Pro-Leu. The peptide with the drug are introduced to the mucosal site in a physical mixture, a conjugated form or by a microcapsule, microsphere, liposome, cell, bacteria, virus or food vesicle carrier by

an oral, nasal, pulmonary, buccal, rectal, transdermal, vaginal or ocular route.

L7: Entry 41 of 42

File: USPT

Jul 9, 1996

DOCUMENT-IDENTIFIER: US 5534496 A

TITLE: Methods and compositions to enhance epithelial drug transport

BSPR:

The entry of high molecular weight active agents (such as peptides, proteins and oligonucleotides) and conventional drugs (such as mannitol, atenolol, fluorescein, insulin, vasopressin, leucine enkephalin, Asu-eel calcitonin, 5-fluorouracil, salicylamide, .beta.-lactones, ampicillin, penicillins, cephalosporins, .beta.-lactamase inhibitors, quinolones, tetracyclines, macrolides, gentamicin, acyclovir, ganciclovir, trifluoropyridine and pentamidine) through mucosal routes (such as oral, nasal, pulmonary, buccal, rectal, transdermal, vaginal and ocular) to the bloodstream is frequently obstructed by poor transport across epithelial cells and concurrent metabolism during transport. Penetration enhancers (substances that facilitate the transport of solute across biological membranes) have been well investigated for the last five decades as reported by Lee et al. (Vincent H. Lee, Akira Yamamoto, and Udaya Bhaskar Kompella, Critical Reviews in Therapeutic Drug Carrier Systems, Vol. 8, No.2, pp. 91-192 (1991), the disclosure of which is herein incorporated by reference). Penetration enhancers are broadly divided into five groups: (1) chelators, e.g. EDTA; (2) surfactants, e.g. sodium lauryl sulfate; (3) bile salts and derivatives, e.g. sodium deoxycholate; (4) fatty acids and derivatives, e.g. oleic acid; and (5) non-surfactants, e.g. unsaturated cyclic ureas. While the penetration enhancers enhance the penneability of the epithelial cell, thereby facilitating the transport of drugs across biological membranes, they also raise a number of pressing safety concerns, such as irritation of mucosal tissues, damages in the mucosal cells, poor damage recovery rates and alterations in mucociliary clearance (Lee et al. at p. 140).

42. Document ID: RU 2157847 C2, GB 2299085 A, AU 9648033 A, WO 9637622 A1, ZA 9602340 A, CA 2172447 A, AU 9651656 A, NO 9704318 A, CZ 9702973 A3, EP 832257 A1, SK 9701256 A3, BR 9607920 A, GB 2299085 B, HU 9802388 A2, KR 98703238 A, AU 715297 B, JP 2000510683 W

L7: Entry 42 of 42

File: DWPI

Oct 20, 2000

DERWENT-ACC-NO: 1996-415084

DERWENT-WEEK: 200105

TITLE: New recombinant DNA coding for bile salt stimulated lipase and secretory signal sequence - controlled by Pichia pastoris promoter allows prodn. of correctly processed lipase in P. pastoris, useful as additive for infant feeds to improve fat absorption

PRIORITY-DATA: 1995SE-0001939 (May 24, 1995), 1995IN-0000351 (March 23, 1995)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
RU 2157847 C2	October 20, 2000	N/A	000	C12N015/55
GB 2299085 A	September 25, 1996	N/A	038	C12N015/81
AU 9648033 A	October 3, 1996	N/A	000	C12N015/81
WO 9637622 A1	November 28, 1996	E	041	C12N015/81
ZA 9602340 A	November 29, 1996	N/A	038	C12N000/00
CA 2172447 A	September 24, 1996	N/A	000	C12N015/81
AU 9651656 A	December 11, 1996	N/A	000	C12N015/81
NO 9704318 A	November 11, 1997	N/A	000	C12N015/55
CZ 9702973 A3	March 18, 1998	N/A	000	C12N015/81
EP 832257 A1	April 1, 1998	E	000	C12N015/81
SK 9701256 A3	May 6, 1998	N/A	000	C12N015/81
BR 9607920 A	June 9, 1998	N/A	000	C12N015/81
GB 2299085 B	March 17, 1999	N/A	000	C12N015/81
HU 9802388 A2	March 1, 1999	N/A	000	

C12N015/81

KR 98703238 A
October 15, 1998
N/A
000
C12N015/81

AU 715297 B
January 20, 2000
N/A
000
C12N015/81

JP 2000510683 W
August 22, 2000
N/A
046
C12N015/09

APPLICATION-DATA:
PUB-NO
APPL-DATE
APPL-NO
DESCRIPTOR

RU 2157847C2
March 12, 1996
1996WO-SE00318
N/A

RU 2157847C2
March 12, 1996
1997RU-0117367
N/A

RU 2157847C2
WO 9637622
Based on

GB 2299085A
March 22, 1996
1996GB-0006023
N/A

AU 9648033A
March 13, 1996
1996AU-0048033
N/A

WO 9637622A1
March 12, 1996
1996WO-SE00318
N/A

ZA 9602340A
March 22, 1996
1996ZA-0002340
N/A

CA 2172447A
March 22, 1996
1996CA-2172447
N/A

AU 9651656A
March 12, 1996
1996AU-0051656
N/A

AU 9651656A
WO 9637622
Based on

NO 9704318A
March 12, 1996
1996WO-SE00318
N/A

NO 9704318A
September 19, 1997
1997NO-0004318
N/A

CZ 9702973A3
March 12, 1996
1996WO-SE00318
N/A

CZ 9702973A3
March 12, 1996
1997CZ-0002973
N/A

CZ 9702973A3
WO 9637622
Based on

EP 832257A1
March 12, 1996
1996EP-0908415
N/A

EP 832257A1
March 12, 1996
1996WO-SE00318
N/A

EP 832257A1
WO 9637622
Based on

SK 9701256A3
March 12, 1996
1996WO-SE00318
N/A

SK 9701256A3
March 12, 1996
1997SK-0001256
N/A

BR 9607920A
March 12, 1996
1996BR-0007920
N/A

BR 9607920A
March 12, 1996
1996WO-SE00318
N/A

BR 9607920A
WO 9637622
Based on

GB 2299085B
March 22, 1996
1996GB-0006023
N/A

HU 9802388A2
March 12, 1996
1996WO-SE00318
N/A

HU 9802388A2
March 12, 1996
1998HU-0002388
N/A

HU 9802388A2
WO 9637622
Based on

KR 98703238A
March 12, 1996
1996WO-SE00318
N/A

KR 98703238A
September 23, 1997
1997KR-0706642
N/A

KR 98703238A
WO 9637622
Based on

AU 715297B
March 13, 1996
1996AU-0048033
N/A

AU 715297B
AU 9648033
Previous Publ.

JP2000510683W
March 12, 1996
1996JP-0535592
N/A

JP2000510683W
March 12, 1996
1996WO-SE00318
N/A

JP2000510683W
WO 9637622
Based on

JP 2000510683 W INT-CL (IPC): C12N 0/00; C12N 1/19; C12N 9/20;

C12N 15/09; C12N 15/55; C12N 15/81; C12R 1/84; C12N 9/20; C12R 1/84; C12R 1/84; C12N 9/20; C12R 1/84; C12N 15/09; C12R 1/84

IN: DAS, G

AB: A new DNA molecule (I) comprises: (a) region (Ia) encoding human bile salt stimulated lipase (BSSL) or an active BSSL variant operably linked to the methanol oxidase promoter of P. pastoris or a functionally equiv. promoter; and (b) a region (Ib) encoding a signal peptide able to direct secretion from transfonned P. pastoris cells attached to the 5'-end of (Ia) operably linked to a promoter as in (a). Also new are: (1) vectors contg. (I); and (2) Pichia cells transformed with these vectors., USE - The transformed cells are used to produce BSSL, or its variants, which are additives for infant feeding formulations that contain relatively large amounts of triglycerides. BSSL is thought to be a main rate limiting factor in fat absorption and growth in infants (esp. if premature)., ADVANTAGE - BSSL can be produced cost effectively in Pichia, and recovered from the culture medium in properly processed form. The yield is at least as good as that achieved in other organisms.,
A new DNA molecule (I) comprises: (a) region (Ia) encoding human bile salt stimulated lipase (BSSL) or an active BSSL variant operably linked to the methanol oxidase promoter of P. pastoris or a functionally equiv. promoter; and (b) a region (Ib) encoding a signal peptide able to direct secretion from transformed P. pastoris cells attached to the 5'-end of (Ia) operably linked to a promoter as in (a). Also new are: (1) vectors contg. (I); and (2) Pichia cells transformed with these vectors., USE - The transformed cells are used to produce BSSL, or its variants, which are additives for infant feeding formulations that contain relatively large amounts of triglycerides. BSSL is thought to be a main rate limiting factor in fat absorption and growth in infants (esp. if premature)., ADVANTAGE - BSSL can be produced cost effectively in Pichia, and recovered from the culture medium in properly processed form. The yield is at least as good as that achieved in other organisms.

L7: Entry 42 of 42

File: DWPI

Oct 20, 2000

DERWENT-ACC-NO: 1996-415084
DERWENT-WEEK: 200105

TITLE: New recombinant DNA coding for bile salt stimulated lipase and secretory signal sequence - controlled by Pichia pastoris promoter allows prodn. of correctly processed lipase in P. pastoris, useful as additive for infant feeds to improve fat absorption

TTX:
NEW RECOMBINATION DNA CODE BILE SALT STIMULATING LIPASE SECRETION SIGNAL SEQUENCE CONTROL PICHIA PROMOTE ALLOW PRODUCE CORRECT PROCESS LIPASE P USEFUL ADDITIVE INFANT FEED IMPROVE FAT ABSORB

09/108 673
AA#21

```
    Set  Items  Description
    ---  -----  -----------
? s bile(w)(salt or salts)

      187197  BILE
      175207  SALT
       86252  SALTS
   S1   14580  BILE(W)(SALT OR SALTS)
? s dna or plasmid or oligonucleotide or nucleotide

     1641854  DNA
      195191  PLASMID
       80825  OLIGONUCLEOTIDE
      401570  NUCLEOTIDE
   S2 1957726  DNA OR PLASMID OR OLIGONUCLEOTIDE OR
NUCLEOTIDE
? s adsorb? or absorb? or uptake

       59315  ADSORB?
      137149  ABSORB?
      452840  UPTAKE
   S3  637394  ADSORB? OR ABSORB? OR UPTAKE
? s oral or colon or colonic or alimentary

      908335  ORAL
      203435  COLON
      113401  COLONIC
       16861  ALIMENTARY
   S4 1165452  ORAL OR COLON OR COLONIC OR ALIMENTARY
? s s1 and s2 and s3

       14580  S1
     1957726  S2
      637394  S3
   S5     42  S1 AND S2 AND S3
? rd

...completed examining records
   S6     26  RD (unique items)
? s s6 and py<1997

Processing
         26  S6
    26677652  PY<1997
   S7     14  S6 AND PY<1997
? t s7/3,ab/1-14


 7/3,AB/1    (Item 1 from file: 5)
DIALOG(R)File  5:Biosis Previews(R)
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09872261  BIOSIS NO.: 199598327179
Role of %%%bile%%% %%%salt%%%-dependent cholesteryl ester
hydrolase in the
 %%%uptake%%% of micellar cholesterol by intestinal cells.
AUTHOR: Shamir Raanan; Johnson William J; Zolfaghari Reza; Lee Hyun
Sook;
 Fisher Edward A(a)
AUTHOR ADDRESS: (a)Dep. Biochem., Med. College Pennsylvania, 2900
Queen
Lane, Philadelphia, PA 19129**USA
JOURNAL: Biochemistry  34 (19):p6351-6358 %%%1995%%%
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The %%%bile%%% %%%salt%%%-dependent cholesteryl
ester hydrolase
 (CEH; EC 3.1.1.13) has been proposed to promote the intestinal absorption
 of both the free and esterified (FC, CE) forms of dietary cholesterol.
 For example, it was recently reported that in the human intestinal cell
 line CaCo2, addition of bovine CEH to the medium increased the
 %%%uptake%%% and intracellular esterification of micellar FC supplied at
 subphysiological concentrations (Lopez-Candales et al. (1993)
 Biochemistry 32, 12085-12089). To test the ability of CEH to promote
 micellar cholesterol %%%uptake%%% in a CaCo2 system under more
 physiological conditions, an in vitro model was developed. Cells stably
 expressing rat CEH were created by %%%DNA%%% transfection (Tr
cells), and
 the %%%uptake%%% of micellar FC and its intracellular esterification
were
 measured using isotopic methods in Tr and control cells. Experimental
 parameters that were varied included micellar composition (monoolein or
 egg PC: FC, CE, or both), the final concentration of micellar cholesterol
 (1 nM to 50 mu-M), the origin of CEH (endogenously synthesized vs
 exogenously added), and the species source of enzyme (rat, pig, man). The
 %%%uptake%%% of cholesterol that was derived from micellar CE was
 significantly increased 5-10-fold (p lt 0.001) in Tr vs control cells as
 a result of the hydrolysis of the CE by the CEH and subsequent
 %%%uptake%%% of the liberated free cholesterol. In contrast, the
 %%%uptake%%% of micellar FC was not increased by the presence of
CEH,
 whether it was endogenous or exogenous. In addition, based on TLC
 analysis of extracted cellular lipids, there was no evidence that CEH
 promoted the esterification of the FC that was taken up. These results
 were independent of cholesterol concentration and the non-sterol
 composition of the micelles. Although in the presence and absence of CEH
 there was comparable %%%uptake%%% of cholesterol by cells after a 4 h
 incubation with a particular type of micelle, micelles containing egg PC
 were not as effective FC donors as those containing monoolein. Overall,
 the data support a role of CEH in modulating the absorption of CE present
 in the intestinal lumen by a mechanism involving the hydrolysis of CE by
 CEH, thereby increasing the FC concentration gradient between the
 micellar and plasma membrane pools and enhancing the passive cellular
 %%%uptake%%% of free cholesterol.

%%%1995%%%


 7/3,AB/2    (Item 2 from file: 5)
DIALOG(R)File  5:Biosis Previews(R)
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09501137  BIOSIS NO.: 199497509507
Functional reconstitution of ATP-dependent transporters from the
 solubilized hepatocyte canalicular membrane.
AUTHOR: Buechler Markus(a); Boehme Matthias; Ortlepp Helga; Keppler
 Dietrich
AUTHOR ADDRESS: (a)Div. Tumor Biochem., Deutsches
Krebsforschungszentrum,
 Im Neuenheimer Feld 280, D-69120 Heidelbe**Germany
JOURNAL: European Journal of Biochemistry  224 (2):p345-352
%%%1994%%%
ISSN: 0014-2956
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The hepatocyte canalicular membrane contains several
 primary-active ATP-dependent export carriers including one for
%%%bile%%%
 %%%salts%%% and one for leukotriene C-4 and related conjugates. The
 molecular identity of both transporters has not been fully elucidated. To
 establish a transport assay that allows the purification and
 identification of the proteins involved in ATP-dependent %%%bile%%%
 %%%salt%%% transport and in leukotriene C-4 transport, we reconstituted
 solubilized hepatocyte canalicular membranes into phospholipid bilayers
 using a rapid dilution method. The proteoliposomes formed exhibited both
 (3H)taurocholate and (3H)leukotriene C-4 %%%uptake%%%, which was
much
 higher in the presence of ATP than in the presence of the
 non-hydrolyzable ATP-analog AdoPP(CH-2)P or in the absence of
 nucleotides. %%%Nucleotide%%% requirement and osmotic sensitivity of
 (3H)taurocholate transport indicates true transport into the vesicle
 lumen. Optimized conditions for reconstitution included the addition of a
 high concentration of an osmolyte (glycerol) and the presence of
 exogenous phospholipids (0.3%) during solubilization. Highest transport
 rates were obtained by reconstitution into acetone/ether-precipitated
 Escherichia coli phospholipid supplemented with 20% cholesterol and by
 use of octylglucoside concentrations between 30 mM and 50 mM.
 Taurocholate transport was non-competitively inhibited by vanadate (K-i =
 39 mu-M). The kinetic parameters of cyclosporin A inhibition (K-i = 2.6
 mu-M for taurocholate and 4.3 mu-M for leukotriene C-4 transport) as well
 as the affinities of taurocholate (Km = 12 mu-M) and leukotriene C-4 (K-m
```

= 0.5 mu-M) in the proteoliposome system indicate that the reconstitution resulted in functionally active transport systems, which are representative of ATP-dependent transport in the intact plasma membrane.

%%%1994%%%

7/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

09019747 BIOSIS NO.: 199497028117
Parallel decrease of Na+-taurocholate cotransport and its encoding mRNA in primary cultures of rat hepatocytes.
AUTHOR: Liang Dana; Hagenbuch Bruno; Steger Bruno; Meier Peter J(a)
AUTHOR ADDRESS: (a)Div. Clin. Pharmacol., Dep. Med., Univ. Hosp., CH-8091 Zurich**Switzerland
JOURNAL: Hepatology 18 (5):p1162-1166 %%%1993%%%
ISSN: 0270-9139
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We investigated the molecular mechanism underlying the progressive loss of Na+-dependent %%%bile%%% %%%salt%%% %%%uptake%%% in primary cultured rat hepatocytes. A specific cDNA probe was used to quantitate the levels of mRNA encoding the Na+-taurocholate-cotransporting polypeptide at various culture times. Hepatocytes were cultured on collagen in the presence of insulin (10-7 mol/L), dexamethasone (10-7 mol/L) and 10% fetal calf serum for up to 72 hr. During this time period the dissociation constant of Na+-dependent taurocholate %%%uptake%%% remained stable (19 to 39 mu-mol/L), whereas the maximum velocity values decreased from 100% at 3 hr to 55%, 22% and 4% at 24, 48 and 72 hr, respectively. Concomitantly the levels of the Na+-taurocholate-cotransporting polypeptide mRNA also decreased from 100% at 3 hr to 41%, 24% and 4% at the later time points. In contrast, Northern hybridization with complementary %%%DNA%%% probes for three common housekeeping gene products revealed a 1.8- to 3.4-fold increase in the levels of mRNA encoding the alpha-subunit of the Na+K+-ATPase, beta-actin and glycerol-3-phosphate dehydrogenase. These data indicate that the loss of Na+-dependent %%%bile%%% %%%salt%%% %%%uptake%%% in primary cultures of rat hepatocytes is caused by decreased levels of its specific mRNA. Hence the studies further confirm that without specific measures (primary) cultured rat hepatocytes reverse their liver-specific phenotype to a more fetal pattern of gene expression.

%%%1993%%%

7/3,AB/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

08467603 BIOSIS NO.: 199344017603
Cloning and expression of a cDNA encoding the chloride dependent sulfobromophthalein (DSP) %%%uptake%%% system of rat liver.
AUTHOR: Jacquemin E(a); Hagenbuch B; Stieger B; Wolkoff A W; Meier P J
AUTHOR ADDRESS: (a)Div. Clin. Pharmacol., Univ. Hosp., Zurich**Switzerland

JOURNAL: Hepatology 16 (4 PART 2):p89A %%%1992%%%
CONFERENCE/MEETING: 43rd Annual Meeting and Postgraduate Course of the American Association for the Study of Liver Diseases, Chicago, Illinois, USA, October 31-November 3, 1992. HEPATOLOGY
ISSN: 0270-9139
RECORD TYPE: Citation
LANGUAGE: English
1992

7/3,AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

08202780 BIOSIS NO.: 000094015053
CHARACTERIZATION OF THE TRANSPORT OF A SYNTHETIC %%%BILE%%% %%%SALT%%% IODINATED CHOLYL-GLYCYL-TYROSINE IN ISOLATED CULTURED RAT HEPATOCYTES
AUTHOR: DEUTSCH J C; IWAHASHI M M; SUTHERLAND E M; MAPOLES J; SIMON F R
AUTHOR ADDRESS: HEPATOBILIARY RESEARCH CENTER, DEP. MEDICINE, B-158, 4200 E. 9TH AVE., DENVER, COLO. 80262.
JOURNAL: HEPATOLOGY 15 (5). 1992. 917-922. %%%1992%%%
FULL JOURNAL NAME: HEPATOLOGY (Baltimore)
CODEN: HPTLD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The %%%uptake%%% of tri-hydroxy conjugated %%%bile%%% %%%salts%%% by hepatocytes is principally by a sodium-dependent carrier. We examined the %%%uptake%%% kinetics of the high-specific-activity, hydroxylated, conjugated %%%bile%%% %%%salt%%% 125I-labeled cholyl-glycyl-tyrosine, to determine whether this synthetic %%%bile%%% %%%salt%%% was transported by the sodium-dependent %%%bile%%% %%%salt%%% system. 125I-labeled cholyl-glycyl-tyrosine was syntheized, and its transport kinetics were studied in freshly cultured rat hepatocytes. %%%Uptake%%% into hepatocytes was time and temperature dependent and was decreased by the inhibitors diisothiocyanodisulfonic acid stilbene, probenecid and carbonyl cyanid chlorophenyl hydrazone, demonstrating carrier mediation and energy dependence. At concentrations of iodinated cholyl-glycyl-tyrosine less than 10 .mu.mol/L, %%%uptake%%% was 27% .+-. 5% sodium dependent, whereas at concentrations from 10 .mu.mol/l to 40 .mu.mol/L %%%uptake%%% was 52% .+-. 4% sodium dependent. The apparent affinity for %%%uptake%%% of 125I-labeled cholyl-glycyl-tyrosine was 8 .+-. 2 .mu.mol/L, and the maximal velocity was 50 .+-. 20 pmol/.mu.g %%%DNA%%%/min. Both taurocholate and indocyanine green inhibited %%%uptake%%% of 125I-labeled cholyl-glycyl-tyrosine. Indocyanine green inhibited the %%%uptake%%% of 125I-labeled cholyl-glycyl-tyrosine (Ki = 10 .mu.m) more effectively than taurocholate (Ki = 20 .mu.m). We conclude that 125I-labeled cholyl-glycyl-tyrosine is not a specific probe for either sodium-dependent %%%bile%%% %%%salt%%% or sodium-independent organic anion carriers, but appears to use both systems in a concentration-dependent manner in cultured rat hepatocytes.

%%%1992%%%

7/3,AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

06184381 BIOSIS NO.: 000086018563
THE EFFECT OF PROTEIN-CALORIE MALNUTRITION ON THE DEVELOPING LIVER
AUTHOR: OPLETA K; BUTZNER J D; SHAFFER E A; GALL D G
AUTHOR ADDRESS: DEP. PEDIATR., HEALTH SCI. CENT., 3330 HOSP. DRIVE N.W., CALGARY, ALBERTA T2N 4N1, CAN.
JOURNAL: PEDIATR RES 23 (5). 1988. 505-508. %%%1988%%%
FULL JOURNAL NAME: Pediatric Research
CODEN: PEREB
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The effects of protein-calorie malnutrition on %%%bile%%% %%%salt%%% metabolism and liver function were studied. Malnutrition was induced in rabbits by combining litters at 7 days of age (13-16 animals)

and results compared to control litters (six-eight animals). At age 29-30 days biliary output from the common bile duct was measured directly for three 1-h periods: under basal conditions, and in response to intravenous infusion of exogenous glycodeoxycholic acid at 0.75 and 1.5 .mu.mol/min/kg, respectively. The %%%bile%%% %%%salt%%% pool size was measured by isotope dilution. Final mean body weight and liver weight were significantly decreased in malnourished animals compared to controls. Liver weight/body weight was also less in the malnourished groups. Total liver %%%DNA%%% and protein content, as well as the protein to %%%DNA%%% ratio, were less in the malnourished animals compared to controls. Bile flow and %%%bile%%% %%%salt%%% secretion were reduced in the malnourished group when calculated per kg body weight on per mg liver %%%DNA%%%. %%%Bile%%% %%%salt%%%-dependent flow did not differ significantly, but %%%bile%%% %%%salt%%%-independent flow was significantly less in malnourished animals. %%%Bile%%% %%%salt%%% pool size was decreased in the malnourished group. These findings indicate tht malnutrition has a greater impact on liver weight than on total body weight in the preweaning period. In addition, malnutrition reduces bile flow, %%%bile%%% %%%salt%%% secretion, and %%%bile%%% %%%salt%%% pool size which, along with the decrease in %%%bile%%% %%%salt%%%-independent flow, may reflect either an impairment of hepatic %%%uptake%%% function or a delay in postnatal development.

%%%1988%%%

7/3,AB/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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04274760 BIOSIS NO.: 000078004302
EFFECT OF DI BUTYRYL CYCLIC AMP ON THE SYNTHESIS OF %%%BILE%%% %%%SALTS%%%
IN ISOLATED HEPATOCYTES FROM RAT
AUTHOR: BOTHAM K M; BOYD G S
AUTHOR ADDRESS: DEP. BIOCHEM., UNIV. EDINBURGH MED. SCH., HUGH-ROBSON BUILD., GEORGE SQUARE, EDINBURGH, LOTHIAN, GREAT BRITAIN EH8 9XD.
JOURNAL: EUR J BIOCHEM 136 (2). 1983. 313-320. %%%1983%%%
FULL JOURNAL NAME: European Journal of Biochemistry
CODEN: EJBCA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The effect of dibutyryl cAMP (Bt2cAMP) on the synthesis of conjugated cholic, chenodeoxycholic and .beta.-muricholic acids was investigated. Hepatocytes were incubated with 1 mM Bt2cAMP for 3 h at 37.degree. C. In cells from rats with a basal rate of %%%bile%%% %%%salt%%% synthesis (soft-diet-fed rats) production of conjugated cholic acid was increased .apprx. 2-fold, synthesis of conjugated chenodeoxycholic acid was increased 10- to 20-fold but formation of its metabolite, conjugated .beta.2-muricholic acid, was decreased by 30-50% in the presence of the cyclic %%%nucleotide%%%. The sum of the amounts of the 3 %%%bile%%% %%%salts%%% produced (total %%%bile%%% %%%salt%%% synthesis) was increased 30-50% by Bt2cAMP. When hepatocytes were prepared from rats in which %%%bile%%% %%%salt%%% synthesis had been stimulated by feeding the %%%bile%%% %%%salt%%% sequestrant, cholestyramine, Bt2cAMP had no effect on conjugated cholic acid synthesis, increased conjugated chenodeoxycholic acid production 3-5 fold and decreased conjugated .beta.-muricholic acid synthesis by .apprx. 50%. Total %%%bile%%% %%%salt%%% synthesis was unchanged. The ratio of the amount of conjugated cholic acid to conjugated chenodeoxycholic acid + conjugated .beta.-muricholic acid produced, an indication of the activity of 7 .alpha.-hydroxycholest-4-en-3-one 12.alpha.-hydroxylase, was raised by Bt2cAMP in hepatocytes from soft-diet-fed but not in those from cholestyramine-fed rats. The effects of the cyclic %%%nucleotide%%% on the synthesis of the 3 %%%bile%%% %%%salts%%% in hepatocytes from soft-diet-fed rats were saturable at a concentration of .apprx. 2 mM. Responses were half-maximal at concentrations of Bt2cAMP varying between 0.5 and 1.5 mM. In hepatocytes from rats with a basal rate of %%%bile%%% %%%salt%%% synthesis Bt2cAMP probably has effects at 3 different stages in the pathway, at the level of cholesterol 7.alpha.-hydroxylase, 7.alpha.-hydroxycholest-4-en-3-one 12.alpha.-hydroxylase and chenodeoxycholic acid 6.beta.-hydroxylase. In cells from rats in which %%%bile%%% %%%salt%%% synthesis has been stimulated only the effect at the chenodeoxycholic acid 6.beta.-hydroxylase level is apparent. Bt2cGMP and Bt2cCMP had no effect on the synthesis of any of the %%%bile%%% %%%salts%%% measured, showing that the effects are specific for Bt2cAMP.
The ratio of the amounts of the 3 %%%bile%%% %%%salts%%% inside the cells to those in the medium was decreased by .apprx. 90% when Bt2cAMP was present in the hepatocyte incubations. This effect was mimicked by Bt2cGMP and to a lesser extent by Bt2cCMP. Bt2cAMP has an effect on the %%%uptake%%% and/or secretion of %%%bile%%% %%%salts%%% in the hepatocytes.

%%%1983%%%

7/3,AB/8 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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06444759 EMBASE No: 1996105699
Hep G2 cells: A model for studies on regulation of human cholesterol 7alpha- hydroxylase at the molecular level
Pandak W.M.; Stravitz R.T.; Lucas V.; Heuman D.M.; Chiang J.Y.L.
Division of Gastroenterology, PO Box 980711,Richmond, VA 23298-0711 United States
American Journal of Physiology - Gastrointestinal and Liver Physiology (AM. J. PHYSIOL. GASTROINTEST. LIVER PHYSIOL.) (United States) 1996,
270/3 33-3 (G401-G410)
CODEN: APGPD ISSN: 0193-1857
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The present study examines the feedback control governing human cholesterol 7alpha-hydroxylase mRNA expression in the human hepatoblastoma cell line, Hep G2. Glycochenodeoxycholate (GCDC) and glycodeoxycholate, hydrophobic %%%bile%%% %%%salts%%%, decreased cholesterol 7alpha-hydroxylase mRNA levels and bile acid synthesis in a concentration-dependent (76 +/- 8%, P < 0.001, and 48 +/- 3%, P < 0.01, respectively) and time-dependent manner. Cholesterol 7alpha- hydroxylase mRNA levels were repressed with a half-maximal inhibitory concentration of <12.5 muM by GCDC and a half-life of 30 min by 100 muM of the bile acid. The addition of actinomycin D (10 mug/ml) alone or in combination with GCDC (100 muM) led to similar concentration- and time- dependent suppression of cholesterol 7alpha-hydroxylase mRNA. Glycocholate (100 muM), not internalized based on lack of %%%uptake%%% of a fluorescent cholate analogue, had no effect on cholesterol 7alpha-hydroxylase mRNA or total bile acid synthesis. In cultures transfected with a rat cholesterol 7alpha-hydroxylase promoter construct, reporter gene activity was decreased (31%, P < 0.01) by GCDC (100 muM). Hep G2 cells maintain the intracellular machinery to express and rapidly regulate human cholesterol 7alpha-hydroxylase by hydrophobic bile acids. These data suggest that Hep G2 cells will support functional studies of the human cholesterol 7alpha-hydroxylase gene.

7/3,AB/9 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

05552363 EMBASE No: 1993320463
Parallel decrease of Nasup +-taurocholate cotransport and its encoding mRNA in primary cultures of rat hepatocytes
Liang D.; Hagenbuch B.; Stieger B.; Meier P.J.
Clinical Pharmacol./Toxicology Div., Department of Medicine, University Hospital,CH-8091 Zurich Switzerland
Hepatology (HEPATOLOGY) (United States) 1993, 18/5 (1162-1166)
CODEN: HPTLD ISSN: 0270-9139
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

We investigated the molecular mechanism underlying the progressive loss of Nasup +-dependent %%%bile%%% %%%salt%%% %%%uptake%%% in primary cultured
rat hepatocytes. A specific cDNA probe was used to quantitate the levels of mRNA encoding the Nasup +-taurocholate-cotransporting polypeptide at various culture times. Hepatocytes were cultured on collagen in the presence of insulin (10sup -sup 7 mol/L), dexamethasone (10sup -sup 7 mol/L) and 10% fetal calf serum for up to 72 hr. During this time period the dissociation constant of Nasup +-dependent taurocholate %%%uptake%%%
remained stable (19 to 39 mumol/L), whereas the maximum velocity values decreased from 100% at 3 hr to 55%, 22% and 4% at 24, 48 and 72 hr, respectively. Concomitantly the levels of the Nasup +-taurocholate-cotransporting polypeptide mRNA also decreased from 100% at 3 hr to 41%, 24% and 4% at the later time points. In contrast, Northern hybridization with complementary %%%DNA%%% probes for three common housekeeping gene
products revealed a 1.8- to 3.4-fold increase in the levels of mRNA encoding the alpha-subunit of the Nasup +Ksup +-ATPase, beta-actin and glycerol-3-phosphate dehydrogenase. These data indicate that the loss of Nasup +-dependent %%%bile%%% %%%salt%%% %%%uptake%%% in primary cultures of
rat hepatocytes is caused by decreased levels of its specific mRNA. Hence the studies further confirm that without specific measures (primary) cultured rat hepatocytes reverse their liver-specific phenotype to a more fetal pattern of gene expression.

7/3,AB/10 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

05017111 EMBASE No: 1992157327
ATP-dependent %%%bile%%%-%%%salt%%% transport in canalicular rat liver
plasma-membrane vesicles
Stieger B.; O'Neill B.; Meier P.J.
Division of Clinical Pharmacology, Department of Medicine, University Hospital,CH-8091 Zurich Switzerland
Biochemical Journal (BIOCHEM. J.) (United Kingdom) 1992, 284/1 (67-74)
CODEN: BIJOA ISSN: 0264-6021
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The present study identifies and characterizes a novel ATP-dependent %%%bile%%%-%%%salt%%% transport system in isolated canalicular rat liver
plasma-membrane (cLPM) vesicles. ATP (1-5mM) stimulated taurocholate %%%uptake%%% into cLPM vesicles between 6- and 8-fold above equilibrium
%%%uptake%%% values (overshoot) and above values for incubations in the absence of ATP. The ATP-dependent portion of taurocholate %%%uptake%%% was
2-fold higher in the presence of equilibrated KNOinf 3 as compared with potassium gluconate, indicating that the stimulatory effect of ATP was not due to the generation of an intravesicular positive membrane potential. Saturation kinetics revealed a very high affinity (K(m) ~ 2.1muM) of the system for taurocholate. The system could only minimally be stimulated by nucleotides other than ATP. Furthermore, it was preferentially inhibited by conjugated univalent %%%bile%%% %%%salts%%%. Further strong inhibitory
effects were observed with valinomycin, oligomycin, 4,4'-di-isothiocyano-2,2'-stilbene disulphonate, sulphobromophthalein, leukotriene Cinf 4 and N-ethylmaleimide, whereas nigericin, vanadate, GSH, GSSG and daunomycin exerted only weak inhibitory effects or none at all. These results indicate the presence of a high-affinity primary ATP-dependent %%%bile%%%-%%%salt%%% transport system in cLPM vesicles. This
transport system might be regulated in vivo by the number of carriers present at the perspective transport site(s), which, in addition to the canalicular membrane, might also include pericanalicular membrane vesicles.

7/3,AB/11 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

02793240 EMBASE No: 1984012199
The effect of dibutyryladenosine 3',5'-monophosphate on the synthesis of %%%bile%%% %%%salts%%% in isolated hepatocytes from rat
Botham K.M.; Boyd G.S.
Department of Biochemistry, University of Edinburgh Medical School, Hugh
Robson Building, Edinburgh, EH8 9XD United Kingdom
European Journal of Biochemistry (EUR. J. BIOCHEM.) (Germany) 1983,
136/2 (313-319)
CODEN: EJBCA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

The effect of dibutyryladenosine 3',5'-monophosphate (Btinf 2cAMP) on the synthesis of conjugated cholic, chenodeoxycholic and beta-muricholic acids has been investigated. Hepatocytes were incubated with 1 mm Btinf 2cAMP for
3 h at 37degreeC. In cells from rats with a basal rate of %%%bile%%% %%%salt%%% synthesis (soft-diet-fed rats) production of conjugated cholic acid was increased about two fold, synthesis of conjugated chenodeoxycholic acid was increased 10-20 fold but formation of its metabolite, conjugated beta-muricholic acid, was decreased by 30-50% in the presence of the cyclic %%%nucleotide%%%. The sum of the amounts of the three %%%bile%%% %%%salts%%% produced (total %%%bile%%% %%%salt%%% synthesis) was increased
30-50% by Btinf 2-cAMP. When hepatocytes were prepared from rats in wich
%%%bile%%% %%%salt%%% synthesis had been stimulated by feeding the %%%bile%%% %%%salt%%% sequestrant, cholestyramine, Btinf 2cAMP had no
effect on conjugated cholic acid synthesis, increased conjugated chenodeoxycholic acid production 3 - 5 fold and decreased conjugated beta-muricholic acid synthesis by about 50%. Total %%%bile%%% %%%salt%%%
synthesis was unchanged. The ratio of the amount of conjugated cholic acid to conjugated chenodeoxycholic + conjugated beta-muricholic acid produced, an indication of the activity of 7alpha-hydroxycholest-4-en-3-one 12alpha-hydroxylase, was raised by Btinf 2cAMP in hepatocytes from soft-diet-fed but not in the those from cholestyramine-fed rats. The effects of the cyclic %%%nucleotide%%% on the synthesis of three %%%bile%%%
%%%salts%%% in hepatocytes from soft-diet-fed rats were found to be saturable at a concentration of about 2 mM. Responses were half-maximal at concentrations of Btinf 2-cAMP varying between 0.5 and 1.5 mM. These results suggest that in hepatocytes from rats with a basal rate of %%%bile%%% %%%salt%%% synthesis Btinf 2-cAMP has effects at three different
stages in the pathway, at the level of cholesterol 7alpha-hydroxylase, 7alpha-hydroxycholest-4-en-3-one 12alpha-hydroxylase and chenodeoxycholine
acid 6beta-hydroxylase. In cells from rats in which %%%bile%%% %%%salt%%%
synthesis has been stimulated only the effect at the chenodeoxycholic acid 6beta-hydroxylase level is apparent. Btinf 2cGMP and Btinf 2-cCMP had no effect on the synthesis of any of the %%%bile%%% %%%salts%%% measured,
showing that the effects are specific for Btinf 2cAMP. The ratio of the amounts of the three %%%bile%%% %%%salts%%% found inside the cells to those
found in the medium was decreased by about 90% when Btinf 2cAMP was present
in the hepatocyte incubations. This effect was mimicked by Btinf 2cGMP and to a lesser extent by Btinf 2-cCMP. These results indicate that Btinf 2-cAMP has an effect on the %%%uptake%%% and/or secretion of

%%%bile%%%
%%%salts%%% in the hepatocytes.

7/3,AB/12 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08849459 96406693
[Hepatic metabolism and transport of bilirubin and other organic anions]
Adachi Y; Kamisako T; Okuyama Y; Miya H
Second Department of Internal Medicine, Kinki University School of Medicine.
Nippon rinsho (JAPAN) Aug %%%1996%%%, 54 (8) p2276-90, ISSN 0047-1852
Journal Code: KIM
Languages: JAPANESE Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL ; English
Abstract
Most of bilirubin, bile acids and other organic anions are preferentially taken up by the liver and excreted into bile. Recently many transporters on the sinusoidal and canalicular membranes of the hepatocytes have been reported for each ligand. complementary %%%DNA%%% was cloned for human
Na+/taurocholate cotransporting polypeptide (NTCP) which mediates sodium
dependent secondary active hepatic %%%uptake%%% of bile acids. For the
hepatic %%%uptake%%% of non-bile acid-organic anions such as bilirubin, at
least 4 transporters are postulated, i.e., bilirubin/BSP binding protein (BBBP), organic anion binding protein (OABP), bilitranslocase, and organic anion transporting polypeptide (OATP). In the hepatocytes, bilirubin is glucuronidated in the endoplasmic reticulum. The gene for UDP-glucuronosyltransferase (UGT) 1 family has been elucidated and differential splicing from several exons 1 (A to J) results in forming isozymes of UGT 1 including bilirubin UGT. At the canalicular membranes, two main ATP-dependent organic anion transporters have been reported, i.e., canalicular %%%bile%%% %%%salt%%% transporter (cBST) for bile acids and
canalicular multispecific organic anion transporter (cMOAT) for non-bile acid organic anions. Recently multidrug resistance protein (MRP) is reported closely related to or identical to cMOAT. These canalicular ATP-dependent transporters are called ABC (ATP-binding cassette) transporters.

7/3,AB/13 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

08245029 95156474
Transmembrane alpha-helix interactions are required for the functional assembly of the Escherichia coli Tol complex.
Lazzaroni JC; Vianney A; Popot JL; Benedetti H; Samatey F; Lazdunski C;
Portalier R; Geli V
Laboratoire de Microbiologie et Genetique Moleculaire, CNRS Universite Lyon I, Villeurbanne, France.
Journal of molecular biology (ENGLAND) Feb 10 %%%1995%%%, 246 (1) p1-7
, ISSN 0022-2836 Journal Code: J6V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
TolQ, TolR and TolA are membrane proteins involved in maintaining the structure of Escherichia coli cell envelope. TolQ and TolR span the inner membrane with three and with one alpha-helical segments, respectively. The tolQ925 mutation (A177V), located in the third putative transmembrane helix of TolQ (TolQ-III), induces cell sensitivity to %%%bile%%% %%%salts%%% and
tolerance towards colicin A but not colicin E1, unlike a null tolQ mutation, which induces tolerance to all group A colicins. Since TolQ is required for colicin A and E1 %%%uptake%%%, in contrast to TolR, which is
necessary only for colicin A, we hypothesized that the tolQ925 mutation might affect an interaction between TolQ and TolR. We therefore searched for suppressor mutations in TolR that would restore cell envelope integrity and colicin A sensitivity to the tolQ925 mutant. Five different tolR alleles were isolated and characterized. Four of these suppressor mutations were found to be clustered in the single putative transmembrane helix of TolR (TolR-I) and one was located at the extreme C terminus of the protein. In addition, we isolated a spontaneous intragenic suppressor localized in the first transmembrane helix of TolQ (TolQ-I). These observations strongly suggest that TolR and TolQ interact via their transmembrane segments. Sequence analysis indicates that Ala177 lies on the alpha-helix face of TolQ-III that, according to its composition and evolutionary conservation, is the most likely to be involved in protein/protein interaction. Energy minimization of atomic models of the wild-type and mutated forms of TolQ-III and TolR-I suggests that the deleterious effect of the A177V substitution arises from a direct steric hindrance of this residue with neighboring transmembrane segments, and that suppressor mutations may alleviate this effect either directly or indirectly, e.g. by affecting the stability of conformational equilibrium of the transmembrane region of the complex.

7/3,AB/14 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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0148229 DBA Accession No.: 93-06281 PATENT
Hepatitis B virus vaccine formulation - large-scale hepatitis B virus recombinant surface antigen production and purification following expression in yeast high cell density culture; may be used in recombinant vaccine
PATENT ASSIGNEE: Amgen %%%1993%%%
PATENT NUMBER: EP 533492 PATENT DATE: 930324 WPI ACCESSION NO.: 93-095752
(9312)
PRIORITY APPLIC. NO.: US 762678 APPLIC. DATE: 910920
NATIONAL APPLIC. NO.: EP 92308534 APPLIC. DATE: 920918
LANGUAGE: English
ABSTRACT: A hepatitis B virus (HBV) vaccine formulation suitable for administration to mammals is claimed comprising an immunologically effective amount of HBV surface antigen (HBsAg) and a %%%bile%%%
%%%salt%%% , preferably Na deoxycholate. Also claimed are: i. a method
for purifying HBsAg for use in a vaccine formulation comprising (a) lysing host cells in which HBsAg is expressed, (b) clarifying the HBsAg-containing lysate, (c) %%%adsorbing%%% the HBsAg to a colloidal
silicate, e.g. Aerosil 380, (d) eluting %%%adsorbed%%% HBsAg from the
colloidal silicate; (e) subjecting the eluted HBsAg to ionexchange chromatography, density gradient centrifugation and gel filtration chromatography, and (f) recovering highly purified bulk HBsAg; ii. a method for C-limited cultivation of a yeast host strain containing an exogenous %%%DNA%%% sequence comprising initially growing the culture
at 20-30 deg and pH 3.5-6 and after the culture reaches an appropriate cell density, reducing the culture temp. to 15 +/- 3 deg. The method (ii.) enables high cell densities and high level expression of an exogenous gene to be achieved. The method of (i.) enables large-scale purification of HBsAg. (33pp)
? ds

Set Items Description
S1 14580 BILE(W)(SALT OR SALTS)
S2 1957726 DNA OR PLASMID OR OLIGONUCLEOTIDE OR NUCLEOTIDE
S3 637394 ADSORB? OR ABSORB? OR UPTAKE
S4 1165452 ORAL OR COLON OR COLONIC OR ALIMENTARY
S5 42 S1 AND S2 AND S3
S6 26 RD (unique items)
S7 14 S6 AND PY<1997
? s s1 and s2 and s4

14580 S1
1957726 S2
1165452 S4
S8 48 S1 AND S2 AND S4
? rd

...completed examining records
S9 32 RD (unique items)
? s s9 and py<1997

Processing
32 S9
26677652 PY<1997
S10 23 S9 AND PY<1997
? t s10/3,ab/1-23

10/3,AB/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08729051 BIOSIS NO.: 199395018402
%%%Bile%%% %%%salt%%%/acid induction of %%%DNA%%% damage in bacterial
cells: Effect of taurine conjugation.
AUTHOR: Zheng Zhi-Ying; Bernstein Carol
AUTHOR ADDRESS: Dep. Microbiol. and Immunol., Coll. Med., Univ. Arizona,
Tucson, Arizona 85724**
JOURNAL: Nutrition and Cancer 18 (2):p157-164 %%%1992%%%
ISSN: 0163-5581
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Bile%%% %%%salts%%% and acids have been implicated in the
etiology of %%%colon%%% cancer, possibly through their ability to cause
%%%DNA%%% damage. Taurine-conjugated and nonconjugated forms of three
%%%bile%%% %%%salts%%% and one bile acid was tested for %%%DNA%%%
repair-inducing potential for cellular toxicity in a recently developed
Escherichia coli chromotest system. The taurine-conjugated forms of
sodium deoxycholate and lithocholic acid had reduced ability to induce
%%%DNA%%% repair. Also the taurine-conjugated form of lithocholic acid
had a reduced lethal effect. These observations suggest that the
biotransformation step, whereby bacteria in the intestine remove the
taurine added to %%%bile%%% %%%salts%%% in the liver, may be significant
in the etiology of %%%colon%%% cancer.

%%%1992%%%

10/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08021706 BIOSIS NO.: 000093066629
%%%BILE%%% %%%SALT%%%-ACID INDUCTION OF %%%DNA%%% DAMAGE IN BACTERIAL AND
MAMMALIAN CELLS IMPLICATIONS FOR %%%COLON%%% CANCER
AUTHOR: KANDELL R L; BERNSTEIN C
AUTHOR ADDRESS: DEP. MICROBIOL. IMMUNOL., COLL. MED., UNIV. ARIZ., TUCSON,
ARIZ. 85724, USA.
JOURNAL: NUTR CANCER 16 (3-4). 1991. 227-238. %%%1991%%%
FULL JOURNAL NAME: Nutrition and Cancer
CODEN: NUCAD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Two %%%bile%%% %%%salts%%%, sodium chenodeoxycholate and sodium
deoxycholate, induced a %%%DNA%%% repair response in the bacterium
Escherichia coli. Similarly, a bile acid and a %%%bile%%% %%%salt%%%,
chenodeoxycholic acid and sodium deoxycholate, induced %%%DNA%%% repair
(indicated by unscheduled %%%DNA%%% synthesis) in human foreskin
fibroblasts. Also, %%%DNA%%% repair-deficient Chinese hamster ovary (CHO)
cells were found to be more sensitive than normal cells to killing by
%%%bile%%% %%%salts%%%. In particular, mutant UV4 CHO cells, defective in
%%%DNA%%% excision repair and %%%DNA%%% cross-link removal, were more
sensitive to sodium chenodeoxycholate, and mutant EM9 CHO cells,
defective in strand-break rejoining, were more sensitive to sodium
deoxycholate than wild-type cells. These results indicate that %%%bile%%%
%%%salts%%%/acid damage %%%DNA%%% of both bacterial and mammalian cells
in vivo. Previous epidemiological studies have shown that %%%colon%%%
cancer incidence correlates with fecal bile acid levels. The findings
reported here support the hypothesis that %%%bile%%% %%%salts%%%/acids
have an etiologic role in %%%colon%%% cancer by causing %%%DNA%%% damage.

%%%1991%%%

10/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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07995823 BIOSIS NO.: 000093051496
CHRONIC EFFECT OF %%%ORAL%%% CHOLESTYRAMINE A %%%BILE%%% %%%SALT%%%
SEQUESTRANT AND EXOGENOUS CHOLECYSTOKININ ON INSULIN RELEASE IN RATS
AUTHOR: KOGIRE M; GOMEZ G; UCHIDA T; ISHIZUKA J; GREELEY G H JR; THOMPSON J
C
AUTHOR ADDRESS: DEP. SURGERY, UNIV. TEX. MED. BRANCH, GALVESTON, TEX.
77550.
JOURNAL: PANCREAS 7 (1). 1992. 15-20. %%%1992%%%
FULL JOURNAL NAME: Pancreas
CODEN: PANCE
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: %%%Oral%%% cholestyramine, a %%%bile%%% %%%salt%%% sequenstant,
stimulates pancreatic exocrine secretion and growth chiefly by increasing
cholecystokinin (CCK) release. In this report, we examine pancreatic
insulin content and insulin release from the isolated perfused pancreas
in rats given %%%oral%%% cholestyramine (4%, wt/wt) or subcutaneous CCK-8
(1 .mu.g/kg every 8 h) for 2 weeks. Cholestyramine significantly
increased pancreatic weight by 32%. CCK administration significantly
increased pancreatic weight by 15%. Total pancreatic content of protein
and %%%DNA%%% were also increased significantly by cholestyramine and
pancreatic protein content was increased significantly by CCK
adminstration. Total pancreatic insulin content was not affected by
cholestyramine or CCK. Both cholestyramine and CCK significantly
increased the first phase of glucose (8.4 mM)-stimulated release of
insulin [mean insulin output (ng/min): control, 2.0 .+-. 0.1:
cholestyramine, 2.7 .+-. 0.2; CCK, 2.6 .+-. 0.2]. Cholestyramine also
significantly enhanced the second phase of glucose-stimulated release of
insulin. Insulin release stimulated by CCK-8 (10-10 M) was not affected
by %%%oral%%% cholestryramine or CCK treatment. These findings indicate
that %%%oral%%% cholestyramine and exogenous CCK have a stimulatory
effect on .beta. cell function. Since pancreatic insulin content was not
affected by cholestyramine and CCK treatment, cholestyramine and CCK may
increase the sensitivity of .beta. cells of glucose. The absence of a
stimulatory effect of cholestyramine and CCK administration on insulin
release in response to CCK-8 may be related to a down-regulation of CCK
receptors on .beta. cells.

%%%1992%%%

10/3,AB/4 (Item 4 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

05161479 BIOSIS NO.: 000082002100
ROLE OF REACTIVE OXYGEN IN %%%BILE%%% %%%SALT%%% STIMULATION OF
%%%COLONIC%%% EPITHELIAL PROLIFERATION
AUTHOR: CRAVEN P A; PFANSTIEL J; DERUBERTIS F R
AUTHOR ADDRESS: VA MED. CENT., UNIVERSITY DR. C, PITTSBURGH, PA. 15240.
JOURNAL: J CLIN INVEST 77 (3). 1986. 850-859. %%%1986%%%
FULL JOURNAL NAME: Journal of Clinical Investigation
CODEN: JCINA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Our previous studies had suggested a link between %%%bile%%% %%%salt%%% stimulation of %%%colonic%%% epithelial proliferation and the release and oxygenation of arachidonate via the lipoxygenase pathway. In the present study, we examined the role of reactive oxygen versus end products of arachidonate metabolism via the cyclooxygenase and lipoxygenase pathways in %%%bile%%% %%%salt%%% stimulation of rat %%%colonic%%% epithelial proliferation. Intracolonic instillation of 5 mM deoxycholate increased mucosal ornithine decarboxylase activity and [3H]thymidine incorporation into %%%DNA%%%. Responses to deoxycholate were abolished by the superoxide dismutase mimetic CuII (3,5 diisopropylsalicylic acid)2 (CuDIPS), and by phenidone or esculetin, which inhibit both lipoxygenase and cyclooxygenase activities. By contrast, indomethacin potentiated the response. Phenidone and esculetin suppressed deoxycholate-induced increases in prostaglandin E2 (PGE2), leukotriene B4 (LTB4), and 5, 12, and 15-hydroxyeicosatetraenoic acid (HETE), whereas CuDIPS had no effect. Indomethacin suppressed only PGE2.
Deoxycholate (0.5-5 mM) increased superoxide dismutase sensitive chemiluminescence 2-10-fold and stimulated superoxide production as measured by cytochrome c reduction in %%%colonic%%% mucosal scrapings or crypt epithelium. %%%Bile%%% %%%salt%%%-induced increases in chemiluminescence were abolished by CuDIPS, phenidone, and esculetin, but not by indomethacin. Intracolonic generation of reactive oxygen by xanthine-xanthine oxidase increased %%%colonic%%% mucosal ornithine decarboxylase activity and [3H]thymidine incorporation into %%%DNA%%% approximately twofold. These effects were abolished by superoxide dismutase. The findings support a key role for reactive oxygen, rather than more distal products of either the lipoxygenase or cyclooxygenase pathways, in the stimulation of %%%colonic%%% mucosal proliferation by %%%bile%%% %%%salts%%%.

%%%1986%%%

10/3,AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

04634922 BIOSIS NO.: 000079047959
%%%BILE%%% %%%SALT%%% STIMULATION OF %%%COLONIC%%% EPITHELIAL PROLIFERATION
EVIDENCE FOR INVOLVEMENT OF LIPOXYGENASE PRODUCTS
AUTHOR: DERUBERTIS F R; CRAVEN P A; SAITO R
AUTHOR ADDRESS: DEPARTMENT MEDICINE AND PATHOLOGY, VETERANS ADMINISTRATION MEDICAL CENTER, SCHOOL MEDICINE, UNIVERSITY PITTSBURGH, PITTSBURGH, PENNSYLVANIA 15240.
JOURNAL: J CLIN INVEST 74 (5). 1984. 1614-1624. %%%1984%%%
FULL JOURNAL NAME: Journal of Clinical Investigation
CODEN: JCINA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Prostaglandin E2 (PGE2) and several other prostaglandins synthesized by the %%%colon%%% suppress the proliferative activity of %%%colonic%%% epithelium. However, %%%bile%%% %%%salts%%% stimulate %%%colonic%%% epithelial proliferation despite the actions of %%%bile%%% %%%salts%%% to enhance the release of arachidonate and consequent %%%colonic%%% synthesis of PGE2. The current study was conducted to assess whether %%%bile%%% %%%salt%%%-induced increases in %%%colonic%%% formation of arachidonate metabolites other than PGE2 were linked to the stimualtion of the proliferative activity of %%%colonic%%% epithelium. Within 10 min of addition, deoxycholate markedly stimulated the in vitro release of [14C]arachidonate from prelabeled rat %%%colon%%%. When given in vivo by intracolonic instillation, deoxycholate (10 .mu.mol) increased %%%colonic%%% accumulation of immunoreactive prostaglandin E (PGE), thromboxane B2 (TXB2), and the lipoxygenase product 12-hydroxyeicosatetraenoic acid (12-HETE) by 2- to 4-fold over control in 30 min. This effect of intracolonic deoxycholate was followed by a 9-fold increase in mucosal ornithine decarboxylase [OD] activity (4 h) and a subsequent 2- to 3-fold increase in [3H]thymidine ([3H]Thd) incorporation into %%%DNA%%% of either mucosal scrapings or isolated pools of proliferative %%%colonic%%% epithelial cells (24 h). Intracolonic instillation of indomethacin (50 .mu.mol) suppressed to low or undetectable levels both basal %%%colonic%%% accumulation of PGE and TXB2 and the increases in each parameter induced by subsequent instillation of deoxycholate. By contrast, indomethacin enhanced accumulation of 12-HETE in both control colons and those subsequently exposed to deoxycholate. The increases in 12-HETE induced by indomethacin alone were correlated with stimulation of mucosal OD activity and [3H]Thd incorporation into mucosal %%%DNA%%%. Indomethacin also enhanced the increases in these parameters induced by deoxycholate. Intracolonic instillation of phenidone (25-100 .mu.mol) suppressed accumulation of PGE, TXB2 and 12-HETE in control colons and the increases in these parameters induced by a subsequent instillation of deoxycholate. Phenidone alone did not alter mucosal OD activity or [3H]thymidine incorporation into mucosal %%%DNA%%%. However, phenidone suppressed or abolished increases in these parameters induced by a subsequent instillation of deoxycholate. 4-(2-[1H-imidazol-1-yl]ethoxy)benzoic acid hydrochloride UK 37,248, which selectively reduced %%%colonic%%% TXB2 to undetectable levels without altering PGE or 12-HETE, had no effect on control or deoxycholate-induced increases in mucosal OD activity or [3H]Thd incorporation into %%%DNA%%%.
Neither indomethacin nor phenidone altered the increases in [14C]arachidonate release induced in vitro by deoxycholate. Chenodeoxycholate and cholate also stimulated [14C]arachidonate release from %%%colon%%% in vitro within 10 min and increased %%%colonic%%% 12-HETE (30 min) and mucosal OD activity (4 h) upon intracolonic instillation. Prior instillation of phenidone inhibited the increases in both 12-HETE and ornithine decarboxylase activity induced by these %%%bile%%% %%%salts%%%. A role for %%%bile%%% %%%salt%%%-induced increases in %%%colonic%%% accumulation of lipoxygenase products, as reflected by 12-HETE, in the subsequent stimulation of the proliferative activity of %%%colonic%%% epithelium is supported.

%%%1984%%%

10/3,AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03980610 BIOSIS NO.: 000076066176
STIMULATION OF DEOXY THYMIDINE INCORPORATION IN THE %%%COLON%%% OF RATS
TREATED INTRA RECTALLY WITH BILE ACIDS AND FATS
AUTHOR: BULL A W; MARNETT L J; DAWE E J; NIGRO N D
AUTHOR ADDRESS: DEP. SURGERY, WAYNE STATE UNIV. MED., WAYNE STATE UNIV., DETROIT, MI 48201, USA.

JOURNAL: CARCINOGENESIS (LOND) 4 (2). 1983. 207-210.
%%%1983%%%
FULL JOURNAL NAME: CARCINOGENESIS (London)
CODEN: CRNGD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The incorporation of [3H] deoxythymidine ([3H]dThd) into %%%colonic%%% %%%DNA%%% of male Sprague-Dawley rats treated intrarectally (i.r.) with %%%bile%%% %%%salts%%% and other substances was investigated. Instillation of sodium deoxycholate caused an increase in the incorporation of [3H]dThd which was maximal 12 h after treatment. The level of incorporation showed a steep linear dose response from 0.5 to 15 mM %%%bile%%% %%%salt%%%. Higher concentrations of deoxycholate up to 300 mM only slightly increased the extent of incorporation when compared to the lower concentration. Several other substances also increased the extent of [3H]dThd incorporation; these include: chenodeoxycholate, lithocholate, sodium dodecyl sulfate, dioctyl sulfosuccinate, corn oil, beef fat and trioctanoin. Substances which had no effect on [3H]dThd incorporation include cholesterol, dehydrocholate, sodium acetate, dextrose and mineral oil. Many of the agents which increase %%%colonic%%% [3H]dThd incorporation are also known to enhance %%%colonic%%% tumorigenesis. Similarites are indicated between the short-term effects, in their respective target tissues, of %%%colon%%% tumor promoters, and classical mouse skin tumor promoters.

%%%1983%%%

10/3,AB/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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03557006 BIOSIS NO.: 000073060087
ROLE OF PROSTAGLANDINS IN %%%BILE%%% %%%SALT%%% INDUCED CHANGES IN RAT %%%COLONIC%%% STRUCTURE AND FUNCTION
AUTHOR: RAMPTON D S; BREUER N F; VAJA S G; SLADEN G E; DOWLING R H
AUTHOR ADDRESS: DEP. MED., UNIV. COLL. LOND. MED. SCH., RAYNE INST., 5 UNIVERSITY ST., LONDON WC1E 6JJ.
JOURNAL: CLIN SCI (LOND) 61 (5). 1981. 641-648. %%%1981%%%
FULL JOURNAL NAME: Clinical Science (London)
CODEN: CSCIA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The role of prostaglandins [PG] in mediating %%%bile%%% %%%salt%%%-induced diarrhea was investigated with a %%%colonic%%% perfusion technique in vivo in rats either untreated or pretreated with the PG synthesis inhibitor, indomethacin. %%%Colonic%%% perfusion with sodium deoxycholate (1 and 2 mmol/l) reduced net water and Na absorption, whereas at a concentration of 5 mmol/l it caused net fluid secretion. Deoxycholate dose-dependently increased protein and %%%DNA%%% output into the perfusion fluid and, at a concentration of 5 mmol/l, produced histological evidence of %%%colonic%%% mucosal damage (mucus release, goblet cell depletion, patchy epitheliolysis and inflammatory cell infiltration); histological change was less with deoxycholate at 2 mmol/l and did not occur at 1 mmol/l. Output of immunoreactive PGE2 into the %%%colonic%%% perfusion fluid rose 8-, 10- and 270-fold after deoxycholate at 1, 2 and 5 mmol/l, respectively. %%%Colonic%%% perfusion with added PGE2, in concentrations 10 times lower (2.8 nmol/l) and 10 times higher (0.28 .mu.mol/l) than those found in the perfusate after deoxycholate at 5 mmol/l did not alter mucosal function or structure. PGE2 in much higher concentration (0.28 mmol/l) reduced net absorption of water and Na increased protein output 3-fold and, as seen with light microscopy, produced excess surface mucus with minimal goblet cell depletion and no tissue damage. Pretreatment with indomethacin reduced the %%%colonic%%% PGE2 output of rats perfused with deoxycholate at 2 and 5 mmol/l by 56 and 87%, respectively, but the %%%bile%%% %%%salt%%% -induced changes in net water and Na transport and %%%DNA%%% output were not significantly affected. The PG synthesis inhibitor reduced protein loss, goblet cell depletion and surface mucus seen after perfusion with deoxycholate at 2 mmol/l, although it did not prevent the more marked structural changes caused by deoxycholate at 5 mmol/l. In rats PG apparently are not important mediators of the deoxycholate-induced impairment of %%%colonic%%% water and electrolyte transport; they may contribute to the mucus secretion and goblet cell depletion produced by perfusion with deoxycholate in concentrations below those causing gross tissue damage, and overt mucosal damage is not an essential prerequisite for PG release.

%%%1981%%%

10/3,AB/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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02667062 BIOSIS NO.: 000067055130
EXPERIMENTAL %%%COLON%%% CANCER
AUTHOR: LAMONT J T; O'GORMAN T A
AUTHOR ADDRESS: DIV. GASTROENTEROL., PETER BENT BRIGHAM HOSP., 721 HUNTINGTON AVE., BOSTON, MASS. 02115, USA.
JOURNAL: GASTROENTEROLOGY 75 (6). 1978. 1157-1169.
%%%1978%%%
FULL JOURNAL NAME: Gastroenterology
CODEN: GASTA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Several potent and specific chemical carcinogens produce in laboratory rodents a very accurate animal model of human %%%colon%%% cancer. The sequence of events leading to %%%colon%%% cancer after administration of dimethylhydrazine involves its metabolic activation in the host to the active carcinogen methyldiazonium, an alkylating agent. The primary effect of the carcinogen in the %%%colonic%%% epithelial cell is methylation of %%%DNA%%%. This is not specific for the %%%colon%%% because methylation of %%%DNA%%% also occurs in the liver and kidney, which are not target organs for dimethylhydrazine. After an initial period of reduced %%%DNA%%% synthesis lasting up to several days, there is a generalized increase in cellular proliferation and a widening of the proliferative zone manifested by the appearance of mitotic figures in the upper third of the crypt and on the surface epithelium. After 2-3 mo. of treatment there is a decrease in goblet cells, hyperplasia of glands, and areas of focal atypia. Microscopic adenocarcinomas and adenomatous polyps appear between 4-6 mo. after starting treatment, and eventually produce rectal bleeding or bowel obstruction. The yield of tumors in this animal model is effected by alteration in dietary fat, administration of %%%bile%%% %%%salts%%% and cholestyramine, and nonspecific %%%colonic%%% injury; the mechanism of these interactions remains unexplained. The animal model provides the opportunity to study the evolution of %%%colon%%% cancer from the initial damage to epithelial cell %%%DNA%%% in the target tissue to the development of an invasive adenocarcinoma. It should be possible to define more carefully the complex alterations of cellular chemistry which characterize the early malignant cell, and in this way devise a biochemical test for the early diagnosis of %%%colon%%% cancer in man. The animal model likewise provides an excellent test system to further study the effects of manipulations of the diet, bacterial flora, or biliary excretions on the incidence of %%%colon%%% cancer. This may prove extremely useful in unraveling the complex role of dietary fat, endogenous sterols and gut bacteria in tumor formation. Experimental immunotherapy and chemotherapy might also be tested in

rodents with %%%colon%%% cancers before clinical trials in humans.

%%%1978%%%

10/3,AB/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02427329 BIOSIS NO.: 000066009872
STIMULATION OF THYMIDINE INCORPORATION IN MOUSE LIVER AND BILIARY TRACT
EPITHELIUM BY LITHO CHOLATE AND DEOXY CHOLATE
AUTHOR: BAGHERI S A; BOLT M G; BOYER J L; PALMER R H
AUTHOR ADDRESS: ROCKEFELLER UNIV., NEW YORK, N.Y. 10021, USA.
JOURNAL: GASTROENTEROLOGY 74 ((2 PART 1)). 1978 188-192.
%%%1978%%%
FULL JOURNAL NAME: Gastroenterology
CODEN: GASTA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Lithocholate produces bile duct and ductular cell hyperplasia, and adenomatous hepatic nodules. The early effects of lithocholate and related %%%bile%%% %%%salts%%% on the liver and biliary tract were investigated by measuring 3H-thymidine (3HTdR) incorporation into %%%DNA%%% after single %%%oral%%% doses of %%%bile%%% %%%salts%%%.
Lithocholate, in doses of 12.5 mg and above, enhanced incorporation of 3HTdR at 28 and 36 h in gallbladder epithelium and at 36 h in hepatocytes. Areas of hepatocellular necrosis, resembling the lesions of peliosis hepatis, occurred with 12.5- and 25-mg doses of lithocholate, but were not seen with deoxycholate, cholate, chenodeoxycholate, ursodeoxycholate or hyodeoxycholate. Deoxycholate, and to a lesser extent cholate, also stimulated 3HTdR incorporation in liver and gallbladder, but chenodeoxycholate did not. Certain bile acids rapidly exert major effects on cell kinetics in the liver and biliary tract, and these effects depend on the structure of the bile acid molecule. Bile duct (organ) hyperplasia induced by lithocholate must depend on additional factors. The stimulation of proliferative activity by certain (particularly secondary) bile acids may have important consequences for tissues and organs exposed to the bile acid pool during its enterohepatic circulation and subsequent excretion via the %%%colon%%%.

%%%1978%%%

10/3,AB/10 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

06705224 EMBASE No: 1996370173
Bile acid activation of the gadd153 promoter and of p53-independent apoptosis: Relevance to %%%colon%%% cancer
Zheng Z.-Y.; Bernstein H.; Bernstein C.; Payne C.M.; Martinez J.D.; Gerner E.W.
Department Microbiology Immunology, College of Medicine, University of Arizona,Tucson, AZ 85724 United States
Cell Death and Differentiation (CELL DEATH DIFFER.) (United Kingdom)
1996, 3/4 (407-414)
CODEN: CDDIE ISSN: 1350-9047
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Bile acids are strongly implicated in the etiology of %%%colon%%% cancer.
Bile acids also induce apoptosis, and this action may be a key to understanding their role in %%%colon%%% cancer. However the mechanism of
bile acid induction of apoptosis is not known. We present evidence of bile acid activation of the gadd153 promoter (a promoter activated by %%%DNA%%%
damaging agents). We also show that bile acid induction of apoptosis is p53-independent. In addition, %%%bile%%% %%%salts%%% were found to induce
blebbing preceding the actual morphological onset of apoptosis, which indicates early cytoskeletal alterations.

10/3,AB/11 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

04353920 EMBASE No: 1990241983
Experimental %%%colonic%%% carcinogenesis after gastric surgery
Houghton P.W.J.; Owen R.J.; Henly P.J.; Mortensen N.J.M.; Hill M.J.; Williamson R.C.N.
University Department of Surgery, Bristol Royal Infirmary, Bristol United Kingdom
British Journal of Surgery (BR. J. SURG.) (United Kingdom) 1990, 77/7 (774-778)
CODEN: BJSUA ISSN: 0007-1323
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Peptic ulcer surgery may predispose to the subsequent development of colorectal cancer. This experimental study has investigated the effects of gastric operations on %%%colonic%%% cell proliferation, bile acid excretion
and carcinogenesis. Male Sprague-Dawley rats (n = 105) underwent sham operation, Polya partial gastrectomy or vagotomy and pyloroplasty. The carcinogen azoxymethane was administered weekly for 6 weeks thereafter (total dose 60 mg kgsup -sup 1). When the animals were killed 24 weeks after operation, colons were examined for mucosal mass, crypt cell production rate (CCPR) and tumour yield; faeces were assayed for contents of neutral steroids and bile acids (both total and individual). Morphometric indices and mucosal %%%DNA%%% content were similar in all
three groups. Polya gastrectomy reduced: (1) CCPR throughout the %%%colon%%% (by 42-65 per cent, P < 0.002); (2) the number of rats with colorectal tumours (26 per cent, P < 0.05); (3) faecal level of neutral steroids and bile acids, notably hyodeoxycholic acid (P < 0.01). Although vagotomy and pyloroplasty increased faecal CCPR, there were no consistent differences in faecal steroids and no alteration in tumour yield after the operation. These results fail to support clinical studies suggesting that gastric surgery predisposes to %%%colonic%%% carcinogenesis. Indeed, Polya
partial gastrectomy exerts a protective effect, probably by inhibiting %%%colonic%%% cell proliferation.

10/3,AB/12 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

04350959 EMBASE No: 1990239022
Reduced cholecystokinin mediates the inhibition of pancreatic growth induced by %%%bile%%% %%%salts%%%
Gomez G.; Townsend Jr. C.M.; Green D.W.; Rajaraman S.; Greeley Jr. G.H.;
Thompson J.C.
Department of Surgery, University of Texas, Medical Branch,Galveston, TX 77550 United States
American Journal of Physiology - Gastrointestinal and Liver Physiology (AM. J. PHYSIOL. GASTROINTEST. LIVER PHYSIOL.) (United States) 1990,
259/1 22-1 (G86-G92)
CODEN: APGPD ISSN: 0002-9513
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The effects of luminal %%%bile%%% %%%salts%%% on plasma levels of cholecystokinin (CCK) and growth of the pancreas in mice were studied. Nonfasting levels of plasma CCK in control mice were 8.1 +/- 1.5 pM. Feeding mice a 0.5% (wt/wt) sodium taurocholate-supplemented diet for 1 wk significantly lowered nonfasting levels of plasma CCK to 4.1 +/- 0.5 pM and decreased the total contents of pancreatic %%%DNA%%% by 22%, RNA by 25%,
and protein by 24%. All of the inhibitory effects of taurocholate on pancreatic growth were comletely reversed by the simultaneous administration of CCK-8 (3 mug/kg, 3 times daily). In contrast, intraluminal neutralization of endogenous %%%bile%%% %%%salts%%% by feeding
a 4% (wt/wt) cholestyramine-supplemented diet for 1 wk significantly

elevated nonfasting levels of plasma CCK to 14.7 +/- 1.5 pM and increased the total contents of pancreatic %%%DNA%%% by 34%, RNA by 40%, and protein
by 35%. All of the stimulatory actions of cholestyramine on pancreatic growth were completely abolished by the administration of the highly potent and specific CCK-receptor antagonist L364,718 (1 mg/kg, twice daily). These findings, therefore, indicate that %%%bile%%% %%%salts%%% appear to play a
physiological role in pancreatic growth by regulation of plasma levels of CCK.

10/3,AB/13 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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03798420 EMBASE No: 1988247860
Role of epidermal growth factor in gastroduodenal mucosal protection
Skov Olsen P.
Department of Surgical Gastroenterology C, Rigshospitalet, 2100 Copenhagen Denmark
Journal of Clinical Gastroenterology (J. CLIN. GASTROENTEROL.) (United
States) 1988, 10/SUPPL. 1 (S146-S151)
CODEN: JCGAD ISSN: 0192-0790
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Epidermal growth factor (EGF) is a polypeptide produced in the submandibular glands, Brunner's glands, and the kidneys. The peptide is secreted in an exocrine fashion into saliva, duodenal juice, and urine. EGF stimulates cellular growth and differentiation and inhibits gastric acid secretion. Removal of the submandibular glands decreases the amount of EGF
in saliva and gastric juice and subsequently the synthesis of %%%DNA%%% in
the gastric mucosa is reduced as well as its resistance to %%%bile%%%-%%%salt%%%-induced gastric lesions. Intragastric instillation of EGF can prevent gastric ulcerations induced by aspirin as well as cysteamine in rats. EGF also accelerates the healing of chronic gastric ulcers induced by acetic acid. Cysteamine is a duodenal ulcerogen in rats. After cysteamine administration, the secretion of EGF from Brunner's glands decreases and the glands become depleted of mucus. Intraduodenal instillation of EGF can partly prevent formation of cysteamine-induced duodenal ulcers. %%%Oral%%%
administration of EGF can accelerate healing of chronic duodenal ulcers in rats. The beneficial effect of EGF on healing of chronic gastroduodenal ulcers is probably due to the delayed effects of EGF such as stimulation of RNA and %%%DNA%%% synthesis. The protective effects of EGF are probably
related to the early actions of the peptide such as activation of cell surface proteins and increased glycosaminoglycan synthesis.

10/3,AB/14 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
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01902666 EMBASE No: 1981145830
Increased cell loss in the human jejunum induced by laxatives (ricinoleic acid, dioctyl sodium sulphosuccinate, magnesium sulphate, %%%bile%%% %%%salts%%%)
Bretagne J.F.; Vidon N.; L'Hirondel Ch.; Bernier J.J.
Unite Rech. Physiopathol. Digest., INSERM U 54, Hop. St-Lazare, Paris France
Gut (GUT) (United Kingdom) 1981, 22/4 (264-269)
CODEN: GUTTA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Two conjugated %%%bile%%% %%%salts%%% (10 mmol/l sodium glycocholate, 10
mmol/l sodium taurodeoxycholate) and three laxatives (30 mmol/l magnesium sulphate, 10 mmol/l ricinoleic acid, 2 mmol/l dioctyl sodium sulphosuccinate) were tested on seven subjects with no intestinal lesions in 14 experiments by intestinal perfusion of the jejunum. A 25 cm segment was studied. Each solution was perfused at the rate of 10 ml/min. Water and electrolyte fluxes, losses of deoxyribonucleic acid (%%%DNA%%%), and intestinal cell enzyme activity were measured in the fluids collected. All the laxatives and %%%bile%%% %%%salts%%% tested (except sodium glycocholate) induced water and electrolyte secretion, a rise in intraluminal %%%DNA%%% loss, and enzyme activity. It was possible to establish a significant correlation ($P < 0.001$) between the amounts of water fluxes and %%%DNA%%% loss under the effect of dioctyl sodium sulphosuccinate and ricinoleic acid.

10/3,AB/15 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
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01457561 EMBASE No: 1979178553
Correlation between %%%bile%%% %%%salt%%%-induced changes of the bowel
habit and intracellular levels of cyclic nucleotides in human %%%colonic%%%
mucosa
Caciagli F.; Corazza G.R.; Ciccarelli R.; et al.
Catt. Farmacol., Fac. Med., Univ. Chieti Italy
Italian Journal of Gastroenterology (ITAL. J. GASTROENTEROL.) (Italy) 1978, 10/1 suppl. (45-46)
CODEN: ITJGD
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

10/3,AB/16 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
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01147791 EMBASE No: 1978278407
Stimulation of thymidine incorporation in mouse liver and biliary tract epithelium by lithocholate and deoxycholate
Bagheri S.A.; Bolt M.G.; Boyer J.L.; Palmer R.H.
Liver Study Unit, Dept. Med., Univ. Chicago, Ill. United States
Gastroenterology (GASTROENTEROLOGY) (United States) 1978, 74/2 I
(188-192)
CODEN: GASTA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Lithocholate produces bile duct and ductular cell hyperplasia, and adenomatous hepatic nodules. The early effects of lithocholate and related %%%bile%%% %%%salts%%% on the liver and biliary tract were investigated by
measuring tritiated thymidine (sup 3HTdR) incorporation into %%%DNA%%%
after single %%%oral%%% doses of %%%bile%%% %%%salts%%%. Lithocholate, in
doses of 12.5 mg and above, enhanced incorporation of sup 3HTdR at 28 and 36 hr in gallbladder epithelium and at 36 hr in hepatocytes. Areas of hepatocellular necrosis, resembling the lesions of peliosis hepatis, occurred with 12.5- and 25-mg doses of lithocholate, but were not seen with deoxycholate, cholate, chenodeoxycholate, ursodeoxycholate, or hyodeoxycholate. Deoxycholate, and to a lesser extent cholate, also stimulated sup 3HTdR incorporation in both liver and gallbladder, but chenodeoxycholate did not. These studies suggest that certain bile acids rapidly exert major effects on cell kinetics in the liver and biliary tract, and that these effects depend on the structure of the bile acid molecule. Bile duct (organ) hyperplasia induced by lithocholate must depend on additional factors. The stimulation of proliferative activity by certain (particularly secondary) bile acids may have important consequences for tissues and organs exposed to the bile acid pool during its enterohepatic circulation and subsequent excretion via the %%%colon%%%.

10/3,AB/17 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
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00274922 EMBASE No: 1975047233
Intestinal secretion
Field M.
Dept. Med., Harvard Med. Sch., Boston, Mass. United States
Gastroenterology (GASTROENTEROLOGY) 1974, 66/5 (1063-1084)

CODEN: GASTA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Intestinal hydrostatic pressure can produce significant alterations of small bowel water and electrolyte transport, but is not ordinarily a cause of fulminant diarrhea. The small bowel epithelium, and probably also the %%%colonic%%% epithelium, possess a cyclic AMP dependent mechanism for
actively secreting water and electrolytes. Cyclic AMP has been shown to inhibit the coupled influx of NaCl across the luminal border. Therefore, in part at least, its effect on water and ion transport in the small bowel can be attributed to an inhibition of an absorptive process. Cyclic AMP may also increase the coupled efflux of NaCl (and perhaps NaHCOinf 3O) across the luminal border, but this has not been established. At present it is uncertain, therefore, whether cyclic AMP only unmasks the presence of active secretion by inhibiting NaCl absorption or whether the %%%nucleotide%%% also stimulates an active secretory process. It is also unresolved whether a single cell type is responsible for both the active absorption and the active secretion of water and electrolytes, or whether 2 different cells are involved. There is no compelling reason to believe, however, that a single cell cannot account for both processes. The clinical importance of these cyclic AMP related transport processes is becoming increasingly apparent. Fulminant watery diarrhea associated with V. cholerae and E. coli organisms results from the activation of testinal mucosal adenyl cyclase by bacterial enterotoxins. The fulminant diarrhea associated with certain hormone secreting tumors probably also involves the intestinal mucosal adenyl cyclase system, although this has not yet been established at the cellular level. There is suggestive evidence that some gastrointestinal hormones, and possibly also prostaglandins and antidiuretic hormones, may play important roles in regulating small intestinal salt and water transport. Whether these hormones, at physiological concentrations, directly affect cyclic AMP metabolism in the intestinal mucosa remains to be determined. Inhibition of absorption or stimulation of secretion in the %%%colon%%% can also contribute to or in itself produce watery diarrhea; the diarrhea associated with %%%bile%%% %%%salt%%% malabsorption and steatorrhea appears to be partially a consequence of direct effects of %%%bile%%% %%%salts%%% and fatty acids on
the %%%colonic%%% mucosa. The similarity of in vitro effects of %%%bile%%%
%%%salts%%% and theophylline suggests stimulation of adenyl cyclase, but this remains to be established at the biochemical level.

10/3,AB/18 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
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00186128 EMBASE No: 1974176261
Hypolipidaemic action of the polysaccharide from Phaseolus mungo (Blackgram). Effect on glycosaminoglycans, lipids and lipoprotein lipase acitivity in normal rats
Menon P.V.G.; Kurup P.A.
Dept. Biochem., Univ. Kerala, Trivandrum India
Atherosclerosis (ATHEROSCLEROSIS) 1974, 19/2 (315-326)
CODEN: ATHSB
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

The polysaccharide from blackgram has been reported to show a cholesterol, phospholipid and triglyceride lowering effect on serum, liver and aorta in rats fed a high fat and high cholesterol diet. The effect of feeding the polysaccharide as the only source of carbohydrate to rats fed an otherwise normal diet, was studied and compared with feeding glucose and sucrose. The polysaccharide produces lower levels of total cholesterol and phospholipids in serum, liver and aorta than does glucose. The triglyceride levels of serum and aorta are comparable in the 2 groups, but lower in the liver in the polysaccharide group. Sucrose, on the other hand, produces higher levels of these lipids in these tissues. Lipoprotein lipase activity is higher in the aorta, liver and heart in the rats fed glucose and polysaccharide, but is considerably decreased in the sucrose group. The individual glycosaminoglycans of the aorta are comparable in both the glucose and polysaccharide group, hyaluronic acid, chondroitin sulfate, A, B, and heparin being slightly raised in the polysaccharide group, while heparan sulfate and chondroitin sulfate C are lower. On the other hand, animals fed sucrose show considerably decreased levels of all these fractions. The levels of soluble protein in the liver and aorta are more or less similar in the polysaccharide and glucose groups, but are decreased in the sucrose group. The hepatic glycogen, however, is lowest in the polysaccharide group and highest in the sucrose group. The fasting blood glucose levels are within the normal range in the animals of the 3 groups, but the level 1 hr after an %%%oral%%% glucose load is higher in the sucrose group. The excretion of faecal sterols and %%%bile%%% %%%salts%%%
is maximum in the polysaccharide group and minimum in the sucrose group.

10/3,AB/19 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08239630 95130268
Apoptosis in colorectal tumour cells: induction by the short chain fatty acids butyrate, propionate and acetate and by the %%%bile%%% %%%salt%%%
deoxycholate.
Hague A; Elder DJ; Hicks DJ; Paraskeva C
CRC Colorectal Tumour Biology Research Group, Bristol, UK.
International journal of cancer. Journal international du cancer (UNITED STATES) Jan 27 %%%1995%%%, 60 (3) p400-6, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The short chain fatty acids acetate, propionate and butyrate are produced when dietary fibre is fermented by the %%%colonic%%% bacteria. We have
previously shown that sodium butyrate induces apoptosis in 3 colorectal tumour cell lines. We have extended our study to 3 adenoma and 4 carcinoma
cell lines and investigated whether propionate and acetate also induce apoptosis. All 3 short chain fatty acids induced apoptosis at physiological concentrations, but of the 3, butyrate was the most effective. Since these fatty acids are produced as a result of bacterial fermentation of dietary fibre, this may in part explain the correlation between a high-fibre diet and low colorectal cancer incidence. Sodium butyrate induced apoptosis in all 7 of the cell lines studied; however, 2 of the 4 carcinoma cell lines (PC/JW/FI and S/KS/FI) were more resistant to butyrate-induced apoptosis than the 3 adenoma cell lines, suggesting that at least some carcinomas may evolve mechanisms to protect the cells from the induction of apoptosis. The bile acid deoxycholic acid has previously been reported as a possible tumour promoter in the large intestine and its levels are reduced by dietary fibre. Concentrations of between 10 nM and 0.1 mM had no effect on either the proliferation or apoptosis of %%%colonic%%% tumour cells in vitro. However, a significant induction of apoptosis was obtained at a concentration of 0.5 mM. These results may have significance for the aetiology of colorectal cancer.

10/3,AB/20 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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06218981 88284193
Role of activation of protein kinase C in the stimulation of %%%colonic%%% epithelial proliferation by unsaturated fatty acids.
Craven PA; DeRubertis FR
Department of Medicine, Veterans Administration Medical Center, Pittsburgh, Pennsylvania.
Gastroenterology (UNITED STATES) Sep %%%1988%%%, 95 (3) p676-85,
ISSN 0016-5085 Journal Code: FH3
Contract/Grant No.: CA 31680, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Some, but not all, studies have suggested that high-fat diets promote %%%colon%%% carcinogenesis, possibly by stimulating the proliferative activity of %%%colonic%%% epithelium. Both the increase in %%%colonic%%%
excretion of %%%bile%%% %%%salts%%% and of fatty acids that occur with an
increase in fat ingestion have been implicated as stimuli of epithelial proliferative activity. In this study, we examined the role of activation of protein kinase C in fatty acid-induced stimulation of %%%colonic%%%
epithelial proliferation in the rat. Intracolonic instillation of

arachidonate, linoleate, or oleate at concentrations that did not induce surface cell injury or loss increased %%%colonic%%% mucosal ornithine decarboxylase activity and stimulated incorporation of [3H]thymidine into mucosal deoxyribonucleic acid. The saturated fatty acid palmitate was without effect. Arachidonate, linoleate, and oleate each induced the translocation of protein kinase C activity from the soluble fraction to the membrane fraction of %%%colonic%%% mucosa, an index of enzyme activation.
The translocation of protein kinase C induced by unsaturated fatty acids occurred both in vivo after intracolonic instillation of these agents and in vitro upon incubation of isolated %%%colonic%%% crypt epithelium with
fatty acids. The effects of the unsaturated fatty acids on both enzyme translocation and %%%colonic%%% epithelial proliferative activity were suppressed by 1-(5-isoquinolinyl)-2-methylpiperazine, an inhibitor of protein kinase C activity. Unsaturated fatty acids directly stimulated soluble %%%colonic%%% mucosal protein kinase C activity when added to the
enzyme assay mixture. This action was blocked by 1-(5-isoquinolinyl)-2-methylpiperazine. However, unsaturated fatty acids also increased the breakdown of polyphosphoinositides when added to isolated %%%colonic%%% epithelium. The increase in polyphosphoinositide
breakdown resulted in release of diacylglycerol, an endogenous activator of protein kinase C. Thus, unsaturated fatty acids may activate protein kinase C of %%%colonic%%% epithelium through either a direct intracellular effect or through an action on the cell membrane. The results support a role for protein kinase C in the stimulation of %%%colonic%%% epithelial proliferation by unsaturated fatty acids.

10/3,AB/21 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05664081 90357205
Gastrointestinal mucus gel rheology.
Sellers LA; Allen A
Department of Physiological Sciences, Medical School, University, Newcastle upon Tyne, UK.
Symposia of the Society for Experimental Biology (ENGLAND) %%%1989%%%, 43 p65-71, ISSN 0081-1386 Journal Code: VGF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Mucus secretions from human and pig stomach; pig duodenum and pig %%%colon%%% have the same viscoelastic gel structure, as determined by
mechanical spectroscopy. These mucus gels are readily solubilised by proteolysis or reduction with thiol agents but are stable with an unchanged mechanical spectra following exposure to pH 1-8, bile, %%%bile%%%
%%%salts%%% and hypertonic 2 M NaCl. Gels of the same mechanical spectra
and stability are reproduced by concentration of the isolated mucins purified free of protein, %%%DNA%%% and lipid (less than 1%). A direct
correlation is observed between percentage of total mucin in polymeric form in the mucus secretion and its gel quality. The mechanical spectra of proteolytically digested mucus, together with the resistance of mucus to denaturing agents suggest carbohydrate-carbohydrate interactions are involved in gel matrix formation. Pig submaxillary mucin forms model gels with the same viscoelastic gel structure as other gastrointestinal gels. Wide variations in the composition and length of the carbohydrate chains of mucins do not affect the gel-forming properties.

10/3,AB/22 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05240920 87093438
[Lipases of the digestive system]
Les lipases du tractus digestif.
Gargouri Y; Pieroni G; Moreau H; Ferrato F; Riviere C; Sauniere JF; Lowe PA; Sarda L; Verger R
Reproduction, nutrition, development (FRANCE) %%%1986%%%, 26 (5B) p1163-76, ISSN 0181-1916 Journal Code: R57
Languages: FRENCH Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW ; English Abstract
Studies on gastrointestinal lipolysis have underestimated several important points. In view of recent in vitro data obtained in our laboratories, this review focuses on the role of gastric lipolysis during fat digestion. Polyclonal antibodies generated from purified rat lingual lipase were used to screen a cDNA library prepared from mRNA isolated from
the serous glands of rat tongue cloned in E. coli expression vectors. A cDNA clone was isolated and the %%%nucleotide%%% and predicted amino acid
sequences obtained. Comparison with the N-terminal amino acid sequence of
the purified enzyme confirmed the identity of the cDNA. The amino acid sequence of rat lingual lipase consisted of 377 residues and showed little homology with porcine pancreatic lipase, apart from a short region containing a serine residue at an analogous position to the Ser 152 of the porcine enzyme. Human gastric lipase activity on tributyrin emulsion was detected only in the presence of amphiphiles. This behaviour was in sharp contrast with the strong inhibitory effect of amphiphiles observed on pure pancreatic lipase. To reveal human gastric lipase activity, amphiphiles must be added to human gastric lipase in order to prevent irreversible interfacial denaturation. Human gastric lipase activity was found to be restricted to triacylglycerol/water surface tensions ranging from 8 to 13 dynes/cm. All amphiphiles which decrease interfacial tension to less than 8 dynes/cm act as irreversible inhibitors of human gastric lipase in the absence or presence of %%%bile%%% %%%salts%%%. Our results confirm that
human gastric lipase is capable of hydrolysing triacylglycerol in the presence of the %%%bile%%% %%%salts%%% concentration prevailing in the
upper small intestine and in the presence of %%%alimentary%%% proteins.
These observations could explain the high dietary lipid absorption observed under pancreatic lipase deficiency.

10/3,AB/23 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03857515 83129833
Stimulation of deoxythymidine incorporation in the %%%colon%%% of rats
treated intrarectally with bile acids and fats.
Bull AW; Marnett LJ; Dawe EJ; Nigro ND
Carcinogenesis (UNITED STATES) %%%1983%%%, 4 (2) p207-10, ISSN
0143-3334 Journal Code: C9T
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The incorporation of tritiated deoxythymidine ([3H]dThd) into %%%colonic%%% %%%DNA%%% of male Sprague-Dawley rats treated intrarectally
(i.r.) with %%%bile%%% %%%salts%%% and other substances has been
investigated. Instillation of sodium deoxycholate caused an increase in the incorporation of [3H]dThd which was maximal 12 h after treatment. The level of incorporation showed a steep linear dose response from 0.5 mM to 15 mM
%%%bile%%% %%%salt%%% . Higher concentrations of deoxycholate up to 300 mM
only slightly increased the extent of incorporation when compared to the lower concentration. Several other substances also increased the extent of [3H]dThd incorporation; these include: chenodeoxycholate, lithocholate, sodium dodecyl sulfate, dioctyl sulfosuccinate, corn oil, beef fat, and trioctanoin. Substances which had no effect on [3H]dThd incorporation include cholesterol, dehydrocholate, sodium acetate, dextrose, and mineral oil. Many of the agents which increase %%%colonic%%% [3H]dThd incorporation
are also known to enhance %%%colonic%%% tumorigenesis. These findings
indicate similarities between the short-term effects, in their respective target tissues, of %%%colon%%% tumor promoters, and classical mouse skin
tumor promoters.
? ds

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Set    Items  Description
S1     14580  BILE(W)(SALT OR SALTS)
S2   1957726  DNA OR PLASMID OR OLIGONUCLEOTIDE OR
NUCLEOTIDE
S3    637394  ADSORB? OR ABSORB? OR UPTAKE
S4   1165452  ORAL OR COLON OR COLONIC OR ALIMENTARY
S5        42  S1 AND S2 AND S3
S6        26  RD (unique items)
S7        14  S6 AND PY<1997
S8        48  S1 AND S2 AND S4
S9        32  RD (unique items)
S10       23  S9 AND PY<1997
? s s7 or s10

          14  S7
          23  S10
   S11    37  S7 OR S10
? log
```